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(71) **Applicant** (*for all designated States except US*): **HUMAN GENOME SCIENCES, INC.** [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).

(72) **Inventors**; and

(75) **Inventors/Applicants** (*for US only*): **NI, Jian** [CN/US];

5502 Manorfield Road, Rockville, MD 20853 (US). **EBNER, Reinhard** [DE/US]; 9906 Shelburne Terrace, #316, Gaithersburg, MD 20878 (US). **LAFLEUR, David, W.** [US/US]; 3142 Quesada Street, N.W., Washington, DC 20015 (US). **MOORE, Paul, A.** [GB/US]; 19005 Leatherbark Drive, Germantown, MD 20874 (US). **OLSEN, Henrik, S.** [DK/US]; 182 Kendrick Place, #24, Gaithersburg, MD 20878 (US). **ROSEN, Craig, A.** [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). **RUBEN, Steven, M.** [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). **SOPPET, Daniel, R.** [US/US]; 15050 Stillfield Place, Centreville, MD 22020 (US). **YOUNG, Paul, E.** [US/US]; 122 Beckwith Street, Gaithersburg, MD 20878 (US). **SHI, Yanggu** [US/US]; 437 West Side Drive, Apt. 102, Gaithersburg, MD 20878 (US). **FLORENCE, Kimberly, A.** [US/US]; 12805 Atlantic Avenue, Rockville, MD 20851 (US). **WEI, Ying-Fei** [CN/US]; 242 Gravatt Drive, Berkeley, CA

*[Continued on next page]*

(54) Title: 207 HUMAN SECRETED PROTEINS

[illegible]

**(57) Abstract:** The present invention relates to the novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

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94705 (US). **FLORENCE, Charles** [US/US]; 12805 Atlantic Avenue, Rockville, MD 20851 (US). **HU, Jing-Shan** [CN/US]; 1247 Lakeside Drive, Apt. 3034, Sunnyvale, CA 94086 (US). **LI, Yi** [CN/US]; 1247 Lakeside Drive, Apt. 3034, Sunnyvale, CA 94086 (US). **KYAW, Hla** [MM/US]; 520 Sugarbush Circle, Frederick, MD 21703 (US). **FISCHER, Carrie, L.** [US/US]; 5810 Hall Street, Burke, VA 22015 (US). **FERRIE, Ann, M.** [US/US]; 120 Fox Run Drive, Tewksbury, MA 01876 (US). **FAN, Ping** [CN/US]; 13 Lake Potomac Court, Potomac, MD 20854 (US). **FENG, Ping** [CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US). **ENDRESS, Gregory, A.** [US/US]; 408 Bridge Road, Florence, MA 01062 (US). **DILLON, Patrick, J.** [US/US]; 1055 Snipe Court, Carlsbad, CA 92009 (US). **CARTER, Kenneth, C.** [US/US]; 11600 Brandy Hall Lane, North Potomac, MD 20878 (US). **BREWER, Laurie, A.** [US/US]; 410 Van Dyke Street, Apt. 115, St. Paul, MN 55119 (US). **YU, Guo-Liang** [CN/US]; 242 Gravatt Drive, Berkeley, CA 94705 (US). **ZENG, Zhizhen** [CN/US]; 410 Shipwrighter Way, Lansdale, PA 19446 (US). **GREENE, John, M.** [US/US]; 872 Diamond Drive, Gaithersburg, MD 20878 (US).

- (74) **Agents:** **HOOVER, Kenley, K.** et al.; C/O Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).

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## 207 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides, polypeptides  
5 encoded by these polynucleotides, antibodies that bind these polypeptides, uses of  
such polynucleotides, polypeptides, and antibodies, and their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a  
10 membrane, human cells and other eucaryotes are subdivided by membranes into many  
functionally distinct compartments. Each membrane-bounded compartment, or  
organelle, contains different proteins essential for the function of the organelle. The  
cell uses "sorting signals," which are amino acid motifs located within the protein, to  
target proteins to particular cellular organelles.

15 One type of sorting signal, called a signal sequence, a signal peptide, or a  
leader sequence, directs a class of proteins to an organelle called the endoplasmic  
reticulum (ER). The ER separates the membrane-bounded proteins from all other  
types of proteins. Once localized to the ER, both groups of proteins can be further  
directed to another organelle called the Golgi apparatus. Here, the Golgi distributes  
20 the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes,  
and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the  
extracellular space as a secreted protein. For example, vesicles containing secreted  
proteins can fuse with the cell membrane and release their contents into the  
25 extracellular space - a process called exocytosis. Exocytosis can occur constitutively  
or after receipt of a triggering signal. In the latter case, the proteins are stored in  
secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly,  
proteins residing on the cell membrane can also be secreted into the extracellular  
space by proteolytic cleavage of a "linker" holding the protein to the membrane.

30 Despite the great progress made in recent years, only a small number of genes  
encoding human secreted proteins have been identified. These secreted proteins

include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical diseases, disorders, and/or conditions by using secreted proteins or the genes that encode them.

### *Summary of the Invention*

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant and synthetic methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting diseases, disorders, and/or conditions related to the polypeptides and polynucleotides, and therapeutic methods for treating such diseases, disorders, and/or conditions. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### *Detailed Description*

#### Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA

preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable  
5 of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many  
10 mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment,  
15 polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain  
20 the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the  
25 nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the  
30 polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig

analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,  
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to  
10 sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon  
15 sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower  
20 percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE,  
25 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress  
30 background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking

reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a  
5 complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotide of the present invention can be composed of any  
10 polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA  
15 that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for  
20 example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide  
25 isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications  
30 can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in

a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or  
5 may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of  
10 covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.  
15 (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)  
20 "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the  
25 present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not  
30 more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)



### **Polynucleotides and Polypeptides of the Invention**

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

5           This gene is expressed primarily in melanocytes and, to a lesser extent, in testes, ovary, kidney and other tissues.

          Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of neural crest derived cells including pigmentation defects, melanoma, reproductive organ defects, and defects of the kidney . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, reproductive, and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. melanocytes, testes, ovary, kidney, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in melanocytes indicates that the protein product of this gene is useful for treating disorders that arise from alterations in the number or fate of neural crest derived cells including cancers such as melanoma and defects of the developing reproductive system.

          Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2512 of SEQ ID NO:11, b is an integer of 15 to 2526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

- 10 ENMICVKCLPQYPEHSKHV (SEQ ID NO:487). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed
- 15 by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in infant brain and fetal lung.

- Polynucleotides and polypeptides of the invention are useful as reagents for
- 20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders of the brain or lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
- 25 the above tissues or cells, particularly of the central nervous and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, lung, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
- 30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant brain and fetal lung indicates that the protein product of this gene is useful for treating or diagnosing disorders associated with abnormal proliferation of cells in the Central nervous system and developing lung. Furthermore, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1117 of SEQ ID NO:12, b is an integer of 15 to 1131, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

ARVAFHLICRYILPTVYCHV (SEQ ID NO:488). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to

these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are  
5 also encompassed by the invention.

This gene is expressed primarily in breast lymph node, and to a lesser extent, in ovarian cancer and chondrosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
10 and for diagnosis of diseases and conditions which include, but are not limited to, immune responses such as inflammation or immune surveillance for tumors. This gene may be important for inflammatory responses associated with tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lymph nodes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such  
20 a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 251 as residues: Lys-45 to Val-50, and/or Lys-69 to Arg-76.

The tissue distribution in breast lymph node indicates that the protein product  
25 of this gene is useful for the treatment or diagnosis of immune responses, including those associated with tumor-induced inflammation. Furthermore, given the tissue distribution, the gene product may also be involved in lymphopoiesis. In a case such as this, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. Protein, as well as, antibodies directed against the protein  
30 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 927 of SEQ ID NO:13, b is an integer of 15 to 941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 4**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: ELVESPGAAGNSARSGNVVC (SEQ ID NO:489). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in T-cells and T-cell lymphomas.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological diseases involving T-cells such as inflammation, autoimmunity, and cancers including T-cell lymphomas. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

tissues or cells, particularly of T-cells and other cells of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
5 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and T-cell lymphomas indicates that the protein product of this gene is useful for diagnosing and treating T-cell based  
10 disorders such as inflammatory diseases, autoimmune disease and tumors including T-cell lymphomas. Furthermore, the tissue distribution indicates that the polypeptides or polynucleotides are useful for the treatment, prophylaxis, and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. Additionally,  
15 expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:14, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

30

## FEATURES OF PROTEIN ENCODED BY GENE NO: 5

This gene is expressed primarily in activated monocytes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, autoimmunity, infection, or disorders involving activation of monocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 253 as residues: Asp-19 to Arg-31.

The tissue distribution indicates that the protein product of this gene is useful for diagnosing or treating diseases that result in activation of monocytes including infections, inflammatory responses or autoimmune diseases. Furthermore, expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:15, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

5           The translation product of this gene shares sequence homology with terminal deoxynucleotidyltransferase which is thought to be important in catalyzing the elongation of oligo- or polydeoxynucleotide chains.

          In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

10   FKKLVNPRXQGIRHEEEAVSWQERR (SEQ ID NO:490). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are  
15   encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

          This gene is expressed primarily in activated human neutrophils, and to a lesser extent in T-cells, primary dendritic cells and bone marrow cells.

20           Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly those of the blood such as leukemia and deficiencies in neutrophils such as neutropenia, and immune system disorders. Similarly,  
25   polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune,  
30   cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,



the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils and other immune cells, combined with the homology to terminal deoxynucleotidyltransferase indicates that the protein product of this gene is useful for the treatment and differential diagnosis of acute leukemias. Alternatively, this gene may function in the proliferation of neutrophils and be useful as a treatment for neutropenia, for example, following neutropenia as a result of chemotherapy. Additionally, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in bone marrow, which is a primary site of definitive hematopoiesis. Expression of this gene product in T cells and primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 647 of SEQ ID NO:16, b is an integer of 15 to 661, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

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The translation product of this gene exhibits a reasonable homology to the human chorionic gonadotropic (HCG) analogue-GT beta-subunit as disclosed in U.S.

Patent No. 5,508,261 and PCT Publication No. WO 92/22568. There is a high degree of conservation of the structurally important cysteine residues between these proteins.

This gene is expressed primarily in IL-1 and LPS induced neutrophils.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid  
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment/diagnosis of diseases of the immune system, since  
20 expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of neutrophils for the treatment of neutropenia, for example following chemotherapy.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30 formula of a-b, where a is any integer between 1 to 539 of SEQ ID NO:17, b is an integer of 15 to 553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 8**

5           This gene is expressed primarily in IL-1 and LPS-induced neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies.

10         Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and  
15         wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
20         NO: 256 as residues: Ser-14 to Pro-22, and/or Leu-43 to Val-53.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment and diagnosis of diseases of the immune system, since expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of  
25         neutrophils for the treatment of neutropenia, for example following chemotherapy.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
30         excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 855 of SEQ ID NO:18, b is an integer of 15 to 869, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 9**

When tested against Jurkat cell lines, supernatants removed from cells expressing this gene activated the NF-kB transcription factor. Thus, it is likely that the protein encoded by this gene activates Jurkat cells by activating a transcriptional factor found within these cells. Nuclear factor kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity.

15 This gene is expressed primarily in IL-1 and LPS induced neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies.

20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and

25 wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 257 as residues: Tyr-22 to His-35.

30 The tissue distribution in neutrophils, combined with the biological activity data suggest that the protein product of this gene is useful for the treatment and/or

diagnosis of diseases of the immune system, since expression is primarily in neutrophils, and thus the translation product of this gene may be useful as a growth factor for the differentiation and/or proliferation of neutrophils for the treatment of neutropenia, for example following chemotherapy.

5           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10           cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 945 of SEQ ID NO:19, b is an integer of 15 to 959, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

20

This gene is expressed primarily in activated T-cells and to a lesser extent in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
25           and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunctions including cancer of the T lymphocytes and autoimmune disorders and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
30           tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph,

serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5           The tissue distribution in activated T-cells indicates that the protein product of this gene is useful for the treatment and/or diagnosis of immune disorders, particularly of T-cell origin, and may act as a growth factor for particular subsets of T-cells such as CD4 positive cells, which would make this a useful therapeutic for the treatment of HIV and other immune compromising illnesses. Furthermore, this gene  
10       product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of AIDS or other immune compromising diseases (e.g. by boosting immune responses).

          Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
15       related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
20       more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1432 of SEQ ID NO:20, b is an integer of 15 to 1446, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

25

          The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

          This gene is expressed primarily in fetal tissues, such as liver/spleen and brain,  
30       as well as in placental tissue.

          Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for the diagnosis of many developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression  
5 of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. fetal, placental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
10 fluid from an individual not having the disorder.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful as a growth factor or differentiation factor for particular cell types in the developing fetus and may be useful in replacement or other types of therapy in cases where the gene is expressed aberrantly. Furthermore, the tissue distribution  
15 indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in  
20 the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and  
25 have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1457 of SEQ ID NO:21, b is an integer of 15 to 1471, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 12

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ISVLXYPHCVVHELPELTAESLEAGDSNQFCWRNLFSCINLLRILNKLTKWKH  
SRTMMLVVFKSAPILKRALKVKQAMMQLYVLKLLKVQTKYLGRQWRKSN  
MKTMSAIYQKVRHRLNDDWAYGNDLDARPWDFQAEECALRANIERFNARR  
YDRAHSNPDFLPVDNCLQSVLGQRVDLPEDFQMNYDLWLEREVFSKPISWEE  
LL (SEQ ID NO:491),  
MRAASPPASASDLIEQQKGRGREHKALIKQDNLDAFNERD  
PYKADDSREEEENDDDNSLEGETFPLERDEVMPPLQHPQTDRLXCPKGLP  
WXPVKREKDIEMFLESSRSKFIGYTLGSDTNTVVGLPRPIHESIHTLKQHKYTS  
IAEVQAQMEEYLRSPISGGEEVEQVPAETLYQGLPSLPQYMIALLKILLA  
AAPTSAKAKTDSINILADVLPPEMPTTVLQSMKLGVDVNRHKEVTVKAISAVLL  
LLLKHFKLNHVYQFEYMAQHLVFANCIPLILKFFNQNMSYTTAKNSISVLDYP  
HCVVHELPELTAESLEAGDSNQFCWRNLFSCINLLRILNKLTKWKHSRTMML  
VVFKSAPILKRALKVKQAMMQLYVLKLLKVQTKYLGRQWRKSNMKTMSAI  
YQKVRHRLNDDWAYGNDLDARPWDFQAEECALRANIERFNARRYDRAHSN  
PDFLPVDNCLQSVLGQRVDLPEDFQMNYDLWLEREVFSKPISWEELLQ (SEQ  
ID NO:492),  
MRAASPPASASDLIEQQKGRGREHKALIKQDNLDAFNERDPYKADDSRE  
(SEQ ID NO:493), EEEENDDDNSLEGETFPLERDEVMPPLQHPQTDRLX  
CPKGLPWX (SEQ ID NO:494), PKVREKDIEMFLESSRSKFIGYTLGSDTNTV  
VGLPRPIHESIHTLKQHKYT (SEQ ID NO:495), SIAEVQAQMEEYLRSPISGG  
EEVEQVPAETLYQGLPSLPQYMIA (SEQ ID NO:496), LLKILLAAAPTSAKAK



TDSINILADVLPEEMPTTVLQSMKLGVDVNRHK (SEQ ID NO:497), EVIVKA  
 ISAVLLLLKHFKLNVYQFEYMAQHLVFANCIPLILKFFNQNI (SEQ ID  
 NO:498),  
 MSYTTAKNSISVLDYPHCVVHELPELTAESLEAGDSNQFCWRNLFSCI (SEQ ID  
 5 NO:499), NLLRILNKLTKWKHSRTMMLVVFKSAPILKRALKVKQ  
 AMMQLYVLKL (SEQ ID NO:500),  
 LKVQTKYLGRQWRKSNMKTMSAIYQKVRH RLNDDWAYGNDLDARP (SEQ  
 ID NO:501), WDFQAEECALRANIERFNARRYDR  
 AHSNPDFLPVDNCLQSVLGQRVDL (SEQ ID NO:502), and  
 10 PEDFQMNYDLWLE REV FSKPISWEELLQ (SEQ ID NO:503). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 15 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

The translation product of this gene shares sequence homology with a *C. elegans* protein (gi|1086830 coded for by *C. elegans* cDNA yk20f8.5).

20 This gene is expressed primarily in T-cells, and to a lesser extent in tumor  
 tissue including glioblastoma, menangioma, and Wilm's tumor.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 25 diseases of the immune system, including autoimmune conditions such as rheumatoid  
 arthritis, inflammatory disorders and cancer. Similarly, polypeptides and antibodies  
 directed to these polypeptides are useful in providing immunological probes for  
 differential identification of the tissue(s) or cell type(s). For a number of disorders of  
 the above tissues or cells, particularly of the immune system, expression of this gene  
 30 at significantly higher or lower levels may be routinely detected in certain tissues or  
 cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g.  
 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell

sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

5 NO: 260 as residues: Thr-9 to Ser-14.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the diagnosis and/or modulation of immune function disorders, including rheumatoid arthritis and inflammatory responses. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other  
10 processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in T cells also strongly indicates a role for this protein  
15 in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1388 of SEQ ID NO:22, b is an integer of 15 to 1402, where both a and b correspond to the positions of nucleotide  
25 residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 13

30 This gene is expressed primarily in placenta, and to a lesser extent in fetal liver and bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for the diagnosis of hematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematological and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver, and bone marrow indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells in the treatment of chemotherapy patients or kidney disease. Furthermore, the tissue distribution in placenta indicates that the protein product of this gene is useful for the diagnosis and/or treatment of vascular or reproductive disorders. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1033 of SEQ ID NO:23, b is an integer of 15 to 1047, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 14

This gene is expressed primarily in stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
15 and for diagnosis of hematopoietic disorders including cancer, neutropenia, anemia, and thrombocytopenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of  
20 this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from  
25 an individual not having the disorder.

The tissue distribution in stromal cells indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells, in particular following chemotherapy treatment. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis  
30 of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture,

bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may  
 5 have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
 10 related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
 15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:24, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 15

The translation product of this gene shares sequence homology with epsilon-COP from *Bos taurus*, which is thought to be important as a component of coatamer, a complex of seven proteins, that is the major component of the non-clathrin  
 25 membrane coat.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MAPPAPGPASGGSGEVDELFDVKNAFYIGSYQQCINEAXXVKLSSPERDVER  
 DVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHESRRDSIVAEL  
 30 DREMSRSXDVTNTTFLMAASTYLHDQNPDAALRALHQGDSLECTAMTVQIL  
 LKLDRLDLARKELKRMQDLDEDATLTQLATAWVSLATGGEKLQDAYYIFQE  
 MADKCSPTLLLLNGQAACHMAQGRWEAAEGLLQEALDKDSGYPETLVNLIV

- LSQHLGKPPEVTNRYLSQLKDAHRSHPIKEYQAKENDFDRLVLQYAPSAEA  
 GPESGP (SEQ ID NO:504),
- RDVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHESRRDS  
 IVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQGDSLECTAM  
 5 TVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWVSLATGGEKLQDAY  
 YIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAEGLLQEALDKDSGYPETL  
 VNLIVLSQHLGKPPEVTNRYLSQLKDAHRSHPIKEYQAKENDFDRLVLQYA  
 PSA (SEQ ID NO:505),
- MAPPAPGPASGGSGEVDLFDVKNAFYIGSYQQCINEAXXVKLSSPER (SEQ  
 10 ID NO:506),
- DVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHES (SEQ  
 ID NO:507),
- RRDSIVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQG (SEQ  
 ID NO:508),
- 15 DSLECTAMTVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWVS (SEQ  
 ID NO:509),
- LATGGEKLQDAYYIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAEG  
 (SEQ ID NO:510),
- LLQEALDKDSGYPETLVNLIVLSQHLGKPPEVTNRYLSQLKDAHRSHPI (SEQ  
 20 ID NO:511), FIKEYQAKENDFDRLVLQYAPSAEAGPELSP (SEQ ID NO:512),  
 RDVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHE (SEQ  
 ID NO:513),
- SRDSIVAELDREMSRSXDVTNTTFLMAASIYLHDQNPDAALRALHQ (SEQ  
 ID NO:514),
- 25 GDSLECTAMTVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWV (SEQ  
 ID NO:515),
- SLATGGEKLQDAYYIFQEMADKCSPTLLLLNGQAACHMAQGRWEAAE (SEQ  
 ID NO:516), GLLQEALDKDSGYPETLVNLIVLSQHLGKPPEVTNRYL (SEQ ID  
 NO:517), SQLKDAHRSHPIKEYQAKENDFDRLVLQYAPSA (SEQ ID NO:518),
- 30 or
- NRYYRESWSLQVPVRNSGSTHASERNGASGPRPGLRRLRGGRRAVRRKERL  
 LHRQLPAVHKR (SEQ ID NO:519). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides of the invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in activated monocytes and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunomodulation, specifically relating to transport problems in these cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in activated monocytes and T-cells combined with the homology to epsilon-COP indicates that the protein product of this gene is useful for treating and/or diagnosing problems with the cellular transport of proteins that may result in immunologic dysfunction. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or

protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1194 of SEQ ID NO:25, b is an integer of 15 to 1208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

The translation product of this gene shares sequence homology with an RNA helicase which is thought to be important in polynucleotide metabolism. The translation product of this contig exhibits good homology to the LbeIF4A antigen of *Leishmania braziliensis*. The LbeIF4A antigen, or immunogenic portions of it, can be used to induce protective immunity against leishmaniasis, specifically *L. donovani*, *L. chagasi*, *L. infantum*, *L. major*, *L. braziliensis*, *L. panamensis*, *L. tropica* and *L. guyanensis*. It can also be used diagnostically to detect *Leishmania* infection or to stimulate a cellular and/or humoral immune response or to stimulate the production of interleukin-12. The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in colon cancer, and to a lesser extent, in pituitary.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of cancers particularly of the colon. Similarly, polypeptides and



antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, expression of this gene at significantly higher or lower levels may be routinely  
5 detected in certain tissues or cell types (e.g. colon, pituitary, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 264 as residues: Glu-93 to Ala-98, Gln-150 to Leu-156, Leu-220 to Leu-231, Leu-268 to Arg-273, Val-324 to Pro-341, Arg-372 to Asn-380, Ser-405 to Gly-410, Phe-426 to Ala-433, Glu-458 to Asp-470, and/or Arg-506 to Ser-547.

The tissue distribution in colon cancer, combined with the homology to RNA  
15 helicase indicates that the protein product of this gene is useful for the development of diagnostic tests for colon cancer or other gastrointestinal or metabolic disorders. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1908 of SEQ ID NO:26, b is an integer of 15 to 1922, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

The translation product of this contig has sequence homology to a cytoplasmic protein that binds specifically to JNK, designated the JNK interacting protein-1 or JIP-1 in *Mus musculus*. JIP-1 caused cytoplasmic retention of JNK and inhibition of JNK-regulated gene expression. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

10       APGXGWRGSLGEPPPPRASLSSDTSALSYDSVKYTLVVDEHAQLELV  
SLRRASETTVTRVTLPPS (SEQ ID NO:520),  
APGXGWRGSLGEPPPPRASLSSDTSALSY (SEQ ID NO:521), or  
DSVKYTLVVDEHAQLELVSLRRASETTVTRVTLPPS (SEQ ID NO:522).

Moreover, fragments and variants of these polypeptides (such as, for example,  
15       fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
encoding these polypeptides ) are encompassed by the invention. Antibodies that  
bind polypeptides of the invention are also encompassed by the invention.

20       Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain, including pituitary, cerebellum,  
frontal cortex, and fetal brain, and to a lesser extent in the cortex or the kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
25       and for diagnosis of the central nervous system disorders including ischemia,  
epilepsy, Parkinson's disease, and schizophrenia. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of  
disorders of the above tissues or cells, particularly of the central nervous system,  
30       expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues or cell types (e.g. brain, kidney, cancerous and wounded  
tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Furthermore, the translation product of this contig may suppress the effects of the JNK signaling pathway on cellular proliferation, including transformation by the Bcr-Abl oncogene.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 265 as residues: Pro-6 to Ser-26, Ala-30 to Asp-41, Gly-55 to Ser-61, Gly-74 to Thr-80, Tyr-117 to Ala-123, Tyr-167 to Asp-172, Ala-212 to Cys-223, and/or Pro-239 to Tyr-244.

The tissue distribution in brain indicates that the protein product of this gene is useful for the enhanced survival and/or differentiation of neurons as a treatment for neurodegenerative disease. Furthermore, the tissue distribution indicates that the translation product of this gene may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1937 of SEQ ID NO:27, b is an integer of 15 to 1951, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

## 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 18

The translation product of this gene shares sequence homology with a liver stage antigen from a protozoan parasite.

This gene is expressed primarily in fetal tissue, and to a lesser extent, in activated T-cells and other immune cells.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities and diseases of immune function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid  
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells, combined with the homology to a protozoan antigen indicates that the protein product of this gene is useful for the treatment  
20 and/or immune modulation of parasitic infections. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30 formula of a-b, where a is any integer between 1 to 3975 of SEQ ID NO:28, b is an integer of 15 to 3989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 19**

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- MKAIGIEPSLATYHHIIRLFDQPGDPLKRSSFIIYDIMNELMGKRFSPKDPDDD  
 KFFQSAMSICSSLRDLELAYQVHGLLKTGDNWKFIGPDQHRNFYYSKFFDLIC  
 LMEQIDVTLKWYEDLIPSA YFPHSQTMHLLQALDVANRLEVIPKIWER (SEQ  
 10 ID NO:523),
- KDSKEYGHTFRSDLREEILMLMARDKHPPQLQVAFADCAADIKSAYESQPIRQ  
 TAQDWPATSLNCIAILFLRAGRTQEA WKMLGLFRKH NKIPRSELLNELMDSA  
 KVSNSPSQAIEVVELASAFSLPICEGLTQRVMSDFAINQEKEALSNTALTSD  
 SDTDSSSDSDSDTSEGK (SEQ ID NO:524),
- 15 MKAIGIEPSLATYHHIIRLFDQPGDPLKRSSFIIYDIMNELMGKRFSPK (SEQ ID  
 NO:525),
- DPDDDKFFQSAMSICSSLRDLELAYQVHGLLKTGDNWKFIGPDQHRNFY  
 (SEQ ID NO:526), YSKFFDLICLMEQIDVTLKWYEDLIPSA (SEQ ID NO:527),  
 YFPHSQTMHLLQALDVANRLEVIPKIWER (SEQ ID NO:528),
- 20 KDSKEYGHTFRSDLREEILMLMARDKHPPQLQVAFADCAADIKSAY (SEQ ID  
 NO:529),
- ESQPIRQTAQDWPATSLNCIAILFLRAGRTQEA WKMLGLFRKH NKIPRSE  
 (SEQ ID NO:530),
- LLNELMDSAKVSNSPSQAIEVVELASAFSLPICEGLTQRVMSDFAIN (SEQ ID  
 25 NO:531), or QEKEALSNTALTSDSDTDSSSDSDSDTSEGK (SEQ ID NO:532).
- Moreover, fragments and variants of these polypeptides (such as, for example,  
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 30 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.  
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

5 This gene is expressed primarily in stromal and CD34 depleted bone marrow cells, and to a lesser extent in tissues of embryonic origin.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of hematopoietic origin including cancers and immune dysfunction.

10 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune,

15 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 267 as residues: Ser-28 to Gln-34.

The tissue distribution in stromal and CD34 depleted bone marrow cells indicates that the protein product of this gene is useful as a growth factor for hematopoietic stem cells or progenitor cells which may be useful in the treatment of

25 chemotherapy patients suffering from neutropenia. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex

30 vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection,

inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
- 10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3721 of SEQ ID NO:29, b is an integer of 15 to 3735, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 20

- In specific embodiments, polypeptides of the invention comprise, or
- 20 alternatively consists of, an amino acid sequence selected from the group:
- MSSDNESDIEDEDLKLELRRLRDKHLKEIQDLQSRQKHEIESLYTKLGKVPPA  
 VIIPPAAPLSGRRRRPTKSKGSKSSRSSSLGNKSPQLSGNL SGQSAASVLHPQQ  
 TLHPPGNIPESGQNQLLQPLKPSPSSDNL YSAFTSDGAISVPSLSAPGQGTSSSTN  
 TVGATVNSQAAQAQPPAMTSSRKGTFTDDLHKLVDNWARDAMNLSGRRGS
- 25 KGHMNYEGPGMARKFSAPGQLCISMTSNLGGAPISAASATSLGHFTKSMCP  
 PQQYGFPATPFGAQWSGTGGPAPQLGQFQPVGTASLQNFNISNLQKSISNPP  
 GSNLRTT (SEQ ID NO:533),
- IQDLQSRQKHEIESLYTKLGKVPPAVIIPPAAPLSGRRRRPTKSKGSKSSRSSSL  
 GNKSPQLSGNL SGQSAASVLHPQQTLHPPGNIPESGQNQLLQPLKPSPSSDNL
- 30 YSAFTSDGAISVPSLSAPGQGT SST (SEQ ID NO:534),
- TSDGAISVPSLSAPGQGTSSSTNTVGATVNSQAAQAQPPAMTSSRKGTFTDDL  
 H (SEQ ID NO:535),

KGHMNYEGPGMARKFSAPGQLCISMTSNLGG SAPISAASATSLGHFTK (SEQ ID NO:536), QPLKPSPSSDNL YSAFTSDGAISVPSLSAPG (SEQ ID NO:537), MSSDNESDIEDEDLKLELRRLRD KHLKEIQDLQSRQKHEIESLYTKLGKVP (SEQ ID NO:538),

- 5 PAVIIPPAAPLSGRRRRPTKSKGSKSSRSSSLGNKSPQLSGNLSGQS (SEQ ID NO:539),

AASVLHPQQTLHPPGNIPESGQNQLLQPLKPSPSSDNL YSAFTSDGAISV (SEQ ID NO:540), PLSAPGQGTSSNTV GATVNSQAAQAQPPAMTSSRKGTFTDDL (SEQ ID NO:541),

- 10 HKLVDNWARDAMNLSGRRGSKGHMNYEGPGMARKFSAPGQLCISMT (SEQ ID NO:542),

SNLGG SAPISAASATSLGHFTKSMCPPQQYGFPATPFGAQWSGTGG (SEQ ID NO:543), and PAPQLGQFQPVGTASLQNFNISNLQKSISNPPGSNLRTT (SEQ ID NO:544). Moreover, fragments and variants of these polypeptides (such as, for

- 15 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

- 20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in fetal liver and tissues associated with the CNS.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
- 25 liver and CNS diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
- 30 types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression



level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 268 as residues: Gln-26 to Lys-34.

5           The tissue distribution in fetal liver and neural tissues indicates that the protein product of this gene is useful for the diagnosis and treatment for liver diseases such as hepatocellular carcinomas and diseases of the CNS. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, 10 liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells), as well as the detection and treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic 15 disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of 20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1653 of SEQ ID NO:30, b is an 25 integer of 15 to 1667, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 21

30

The translation product of this gene shows sequence homology to two recently cloned genes, karyopherin beta 3 and Ran\_GTP binding protein 5. (See Genbank

Accession Nos. gi|2102696 and gnl|PID|e328731.) The Ran\_GTP binding protein is related to importin-beta, the key mediator of nuclear localization signal (NLS)-dependent nuclear transport. Based on homology, it is likely that this gene may demonstrate activity similar to the RAN\_GTP binding protein.

5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
VRVAAAESMXLLLECAAXVRGPEYLTQMWHFMCDALIKAIGTEPDSVDLSEI  
MHSFAK (SEQ ID NO:545). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%,  
10 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the  
15 invention.

This gene is expressed in thymus tissue, and to a lesser extent in stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
20 immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
25 types (e.g. immune, thymus, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in thymus indicates that the protein product of this gene is useful for the diagnosis and treatment for immune disorders. Furthermore, the polypeptides or polynucleotides of the present invention are also useful in the

treatment, prophylaxis, and detection of thymus disorders, such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism, and hypothyroidism. Additionally, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1394 of SEQ ID NO:31, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 22

The translation product of this gene shares sequence homology with a natural resistance-associated macrophage protein 2 from Homo sapiens (gi|3152690 (AF064484)), which is thought to function as a macrophage-specific membrane transport protein. This gene is expressed primarily in prostate and osteoclastoma tissues. In specific embodiments, polypeptides of the invention comprise, or

alternatively consists of, an amino acid sequence selected from the group:

MEINNQNCFIVIDLVRTVMENGVEGLLIFGAFLPESWLIGVRCSSPEPKALLIL  
AHSQKRRLDGWSFIRHLRVHYCVSLTIHFS (SEQ ID NO:546),

GGREANKXFFIESCIALFVSFIINVFVVSVFAEXFFGXTNEQVVEVCTNTSSPH

5 AGLFPKDNSTLAVDIYKGGVVLGCYFGPAALYIWAVGILAAGQSST (SEQ ID  
NO:547), GGREANKXFFIESCIALFVSFIINVFVVSVFAEXFFGXTNEQVVE

(SEQ ID NO:548), and/or

VCTNTSSPHAGLFPKDNSTLAVDIYKGGVVLGCYFGPAALYIWAVGILAAGQ  
SST (SEQ ID NO:549). Moreover, fragments and variants of these polypeptides

10 (such as, for example, fragments as described herein, polypeptides at least 80%, 85%,  
90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides ) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the

15 invention. Polynucleotides encoding these polypeptides are also encompassed by the  
invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome  
12. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 12.

20 This gene is expressed primarily in fetal liver/spleen, fetal brain, and to a  
lesser extent in placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
25 immune, developmental, hepatic, or bone and prostate diseases, and cancers,  
particularly of the bone and prostate. Similarly, polypeptides and antibodies directed  
to these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the bone and prostate systems, expression of this gene  
30 at significantly higher or lower levels may be routinely detected in certain tissues or  
cell types (e.g. bone, prostate, cancerous and wounded tissues) or bodily fluids (e.g.  
lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell

sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone indicates that the protein product of this gene is  
5 useful for the diagnosis and treatment of bone and prostate disorders, especially  
cancers of those systems. Elevated levels of expression of this gene product in  
osteoclastoma indicates that it may play a role in the survival, proliferation, and/or  
growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such  
conditions as osteoporosis. Moreover, the protein product of this gene is useful for  
10 the treatment and diagnosis of hematopoietic related disorders such as anemia,  
pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are  
important in the production of cells of hematopoietic lineages. The uses include bone  
marrow cell ex vivo culture, bone marrow transplantation, bone marrow  
reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may  
15 also be involved in lymphopoiesis, therefore, it can be used in immune disorders such  
as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene  
product may have commercial utility in the expansion of stem cells and committed  
progenitors of various blood lineages, and in the differentiation and/or proliferation of  
various cell types. Protein, as well as, antibodies directed against the protein may  
20 show utility as a tumor marker and/or immunotherapy targets for the above listed  
tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
available and accessible through sequence databases. Some of these sequences are  
related to SEQ ID NO:32 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically  
excluded from the scope of the present invention. To list every related sequence is  
cumbersome. Accordingly, preferably excluded from the present invention are one or  
more polynucleotides comprising a nucleotide sequence described by the general  
formula of a-b, where a is any integer between 1 to 3172 of SEQ ID NO:32, b is an  
30 integer of 15 to 3186, where both a and b correspond to the positions of nucleotide  
residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 23**

5 This gene shares sequence homology with the FK506-binding protein (FKBP-  
13) family, a known cytosolic receptor for the immunosuppressants FK506 and rapamycin. Recently, another group has cloned a very similar gene, recognizing the homology to the FK506-binding protein family, calling their gene FKBP23 (See Genbank Accession No. 2827255.). Contact of cells with supernatant expressing the product of this gene increases the permeability of both prostate stromal cells and  
10 dermal fibroblasts to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds receptors on the surface of stromal cells and dermal fibroblast cells. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating stromal and fibroblast cells.

15 This gene is expressed primarily in lymphoid tissues and stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample, especially for those susceptible to immune suppressant therapies and for diagnosis of diseases and conditions which include, but are not limited to, immune suppressant  
20 disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune,  
25 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 271 as residues: Ala-19 to Val-31, Arg-38 to Gly-49, Ala-61 to Lys-66, Tyr-68

to Pro-78, Gly-116 to Ala-121, Asp-154 to Ser-162, Glu-173 to Gln-186, Phe-194 to Gly-203, and/or Pro-207 to Val-212.

The tissue distribution in lymphoid tissues and stromal cells, the biological activity data, combined with the homology to FKBP-12 and -13 indicates that the  
5 protein product of this gene is useful for the diagnosis and treatment of immune suppressant disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of  
10 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:33, b is an  
15 integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 24

20

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in the brain and in the retina.

25

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and ocular associated disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
30 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the central nervous system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 272 as residues: Cys-34 to Asp-40.

10 The tissue distribution in retina indicates that the protein product of this gene is useful for the treatment and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma. Expression in the brain indicates a role in the is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1778 of SEQ ID NO:34, b is an integer of 15 to 1792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 25**

30 This gene shows sequence homology to a newly identified class of proteins expressed in the nervous system, called stathmin family. (See Genbank Accession No. 2585991; see also Eur. J. Biochem. 248 (3), 794-806 (1997).) The stathmin



family appears to be an ubiquitous phosphoprotein involved as a relay integrating various intracellular signaling pathways. These pathways affect cell proliferation and differentiation.

- In specific embodiments, polypeptides of the invention comprise, or  
5 alternatively consists of, an amino acid sequence selected from the group:  
QDKHAEVRKNKELKEEASR (SEQ ID NO:550),  
QQDLSPWAAPVGCPLXXASXTCHXLPLSGCLRRQSXSPLPVVAXLCFWFSCPL  
ASLFVPGQPCVTCPPSLPFQDKHAEVRKNKELKEEASR (SEQ ID NO:551).  
Moreover, fragments and variants of these polypeptides (such as, for example,  
10 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
encoding these polypeptides ) are encompassed by the invention. Antibodies that  
bind polypeptides of the invention are also encompassed by the invention.  
15 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed highly in brain tissues.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
20 neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
25 types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 30 The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease,

schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 882 of SEQ ID NO:35, b is an integer of 15 to 896, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 26

The polynucleotide sequence of this gene contains a domain similar to a Flt3 ligand peptide.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
PTRCCTTQPCRSSARRPCWVPMVPSPEGREXQPTCPs (SEQ ID NO:552).  
Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene may have activity as binding to Flt3 receptors, a process known to promote angiogenesis and/or lymphangiogenesis.

This gene is expressed in human tonsil, and to a lesser extent in teratocarcinoma, placenta, colon carcinoma, and fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the tonsil, as well as cancers, such as colon, reproductive, and kidney  
5 cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tonsils, colon, reproductive organs, and kidneys, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
10 tissues or cell types (e.g. immune, tonsils, colon, kidney, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 274 as residues: Pro-22 to Glu-33.

The tissue distribution in tonsils, several cancers, and fetal tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of diseases of the tonsil or colon, such as tonsillitis, inflammatory diseases involving  
20 nose and paranasal sinuses, especially during the infection of influenza, adenoviruses, parainfluenza, or rhinoviruses, for example. The gene may also be useful in the diagnosis and treatment of neoplasms of nasopharynx or colon origins. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 898 of SEQ ID NO:36, b is an

integer of 15 to 912, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MKRSLNENSARSTAGCLPVPLFNQKKRNRQPLTSNPLKDDSGISTPSDNYDFP  
 10 PLPTDWAWEAVNPEXAPVMKTVDTGQIPHSVSRPLRSQDSVFNSIQSNTGRS  
 QGGWSYRDGNKNTSLKTWXXKNDFKPQCKRTNLVANDGKNSCPMSSGAQQ  
 QKQLRTPEPPNLSRNKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNFQQN  
 QYKXQMLDDIPEDNTLKETSLYQLQFKEKASSLRISAVIESMKYWREHAQKT  
 VLLFEVLAVLDSAVTPGPYYSKTFLMRDGKNTLPCVFYEIDRELRLIRGRVH  
 15 RCVGNYDQKKNIFQCVSVRPASVSEQKTFQAFVKIADVEMQYYINVMNET  
 (SEQ ID NO:553),  
 SQDSVFNSIQSNTGRSQGGWSYRDGNKNTSLKTWXXKNDFKPQCKR (SEQ ID  
 NO:554), NKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNF (SEQ ID  
 NO:555),  
 20 SSLRIISAVIESMKYWREHAQKTVLLFEVLAVLDSAVTPGPYYSKTFLM (SEQ  
 ID NO:556), and/or  
 PRLIRGRVHRCVGNYDQKKNIFQCVSVRPASVSEQKTFQAFV (SEQ ID  
 NO:557). Moreover, fragments and variants of these polypeptides (such as, for  
 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
 25 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by  
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.  
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 This gene is expressed primarily in human testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive disorders, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testes indicates that the protein product of this gene is useful as a hormone with reproductive or other systemic functions; contraceptive development; male infertility of testicular causes, such as Klinefelter's syndrome, varicocele, orchitis; male sexual dysfunctions; testicular neoplasms; and inflammatory disorders such as epididymitis. Furthermore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:37, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in apoptotic T-cell.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases relating to T cells, as well as cancer in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
15 disorders of the above tissues or cells, particularly of the disorders of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such  
20 a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in apoptotic T-cells indicates that the protein product of this gene is useful for the detection and/or treatment of disorders of the immune system. Moreover, since the gene was isolated from an apoptotic cell, and based on  
25 the understanding of the relationship of apoptosis and cancer, it is likely that this gene may play a role in the genesis of cancer. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:38, b is an integer of 15 to 872, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 29**

10

This gene is expressed primarily in human tonsils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25

The tissue distribution in human tonsils indicates that the protein product of this gene is useful for the diagnosis and treatment of gastrointestinal diseases.

Alternatively, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and treatment of a variety of immune system disorders.

Expression of this gene product in tonsils indicates a role in the regulation of the

30

proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or
- 10 proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
- 15 related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
- 20 formula of a-b, where a is any integer between 1 to 798 of SEQ ID NO:39, b is an integer of 15 to 812, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO:30**

- 25 This gene is expressed primarily in human T-cells, and to a lesser extent, in human colon carcinoma.

The translation product of this gene shares sequence homology with C44C1.2 gene product of *Caenorhabditis elegans*.

- Preferred polypeptides of the present invention comprise, or alternatively
- 30 consist of, one, two, three, four, five, six, seven or all seven of the immunogenic epitopes shown in SEQ ID NO:278 as residues: Leu-21 to Ala-30, Ser-38 to Asp-47, Pro-87 to Asp-94, Leu-197 to Thr-204, Pro-256 to Ser-262, Thr-277 to Arg-282,



and/or Thr-293 to Trp-303. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

Additionally, preferred polypeptides of the present invention comprise, or  
 5 alternatively consist of, one, two, or both of the immunogenic epitopes shown in SEQ ID NO:1232 as residues: Gly-204 to Gly-234 and Arg-202 to Asp-236.

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides.

In additional nonexclusive embodiments, preferred polypeptides of the  
 10 invention also comprise, or alternatively consist of, one or more of the following amino acid sequences: Gly-188 to Val-203, Gly-188 to Thr-204, Thr-204 to Lys-257, Asp-280 to Leu-362 of SEQ ID 278 and Gly-204 to Gly-234 of SEQ ID NO: 1232. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

GVFRPCVCGRPASLTCSPLDPEVGPYCDTPTMRTLNFNLLWLALACSPVHTTLS  
 KSDAKKAASKTLLEKSQFSDKPVQDRGLVVTDLKAESVVLEHRSYCSAKAR  
 DRHFAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQLKRRGREMFEVT  
 20 GLHDVDQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELSK  
 TVVQVAKNQHFDFGVVEVWNQLLSQKRVGLIHMLTHLAEALHQARLLALL  
 VIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSLMTYDYSTAHPGPNAPLSWV  
 RACVQVLDPKXKWRTKSSWGSTSMXWTXRPXDARXPVVGXRQIXLKD  
 XPRMVLDSKPQ (SEQ ID NO:558),  
 25 TCSPLDPEVGPYCDTPTMRTLNFNLLWLALACSPVHTTLS (SEQ ID NO:559),  
 LVVTDLKAESVVLEHRSYCSAKARDRHFAGDVLGYVTPWNSHGYDVTKVF  
 GSKF (SEQ ID NO:560),  
 REMFEVTGLHDVDQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSE  
 DE (SEQ ID NO:561),  
 30 HFDGVVEVWNQLLSQKRVGLIHMLTHLAEALHQARLLALLVIPPAITPGTD  
 QLGM (SEQ ID NO:562), and  
 DGFSLMTYDYSTAHPGPNAPLSWVRACVQVLDPKXKWRTKSSWGST (SEQ

ID NO:563). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
5 encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In additional nonexclusive embodiments, polynucleotides of the invention comprise or alternatively consist of, one or more of the following sequences:

10 GGCACGAGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCC  
TGACATGCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCT  
ACCATGCGGACACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCT  
GTTCACTACCCTGTCAAAGTCAGATGCCAAAAAGCCGCCTCAAAGAC  
GCTGCTGGAGAAGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGT  
15 TGGTGGTGACGGACCTCAAAGCTGAGAGTGTGGTTCTTGAGCATCGCAGC  
TACTGCTCGGCAAAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGG  
CTATGTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTG  
GGAGCAAGTTCACACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGT  
GGCCGTGAGATGTTTGAGGTCACGGGCCTCCACGACGTGGACCAAGGGTG  
20 GATGCGAGCTGTCAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGC  
TCCTGTTTGAGGACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTG  
AGGATGAGATAGAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAA  
CCAGCATTTGATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCC  
AGAAGCGCGTGGGCCTCATCCACATGCTCACCCACTTGGCCGAGGCTCTG  
25 CACCAGGCCCGGCTGCTGGCCCTCCTGGTCATCCCGCCTGCCATCACCCCC  
GGGACCGACAGCTGGGCATGTTACGCACAAGGAGTTTGAGCAGCTGGC  
CCCCGTGCTGGATGGTTTCAGCCTCATGACCTACGACTACTCTACAGCGCA  
TCAGCCTGGCCCTAATGCACCCCTGTCCTGGGTTCGAGCCTGCGTCCAGGT  
CCTGGACCCGAAGTCCAAGTGGCGAAGCAAAATCCTCCTGGGGCTCAACT  
30 TCTATGGTACATCCAGACACTGAAGGACCACAGGCCCGGATGGTGTGGG  
ACAGCCAGGTCTCAGAGCACTTCTTCGAGTACAAGAAGAGCCGCAGTGGG  
AGGCACGTGCTCTTCTACCCAACCCTGAAGTCCCTGCAGGTGCGGCTGGA

GCTGGCCCCGGGAGCTGGGCGTTGGGGTCTCTATCTGGGAGCTGGGCCAGG  
GCCTGGACTACTTCTACGACCTGCTCTAGGTGGGCATTGCGGCCTCCGCGG  
TGGACGTGTTCTTTTCTAAGCCATGGAGTGAGTGAGCAGGTGTGAAATAC  
AGGCCTCCACTCCGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
5 AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1228),  
GCGCTGGAGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCCTGAC  
ATGCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCTACCA  
TGCGGACACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCTGTTT  
ACACTACCCTGTCAAAGTCAGATGCCAAAAAGCCGCCTCAAAGACGCTG  
10 CTGGAGAAGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGTTTGGT  
GGTGACGGACCTCAAAGCTGAGAGTGTTGTTCTTGAGCATCGCAGCTACT  
GCTCGGCAAAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGGCTAT  
GTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTGGGAG  
CAAGTTCACACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGTGGCC  
15 GTGAGATGTTTGAGGTCACGGGCCTCCACGACGTGGACCAAGGGTGGATG  
CGAGCTGTCAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGCTCCT  
GTTTGAGGACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTGAGG  
ATGAGATAGAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAACCA  
GCATTTTCGATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCCAGA  
20 AGCGCGTGACCGACCAGCTGGGCATGTTACGCACAAGGAGTTTGAGCAG  
CTGGCCCCCGTGCTGGATGGTTTCAGCCTCATGACCTACGACTACTCTACA  
GCGCATCAGCCTGGCCCTAATGCACCCCTGTCCTGGGTTTCGAGCCTGCGTC  
CAGGTCCTGGACCCGAAGTCCAAGTGGCGAAGCAAAATCCTCCTGGGGCT  
CAACTTCTATGGTATGGACTACGCGACCTCCAAGGATGCCCCTGAGCCTG  
25 TTGTCGGGGCCAGGTACATCCAGACACTGAAGGACCACAGGCCCGGATG  
GTGTGGGACAGCCAGGYCTCAGAGCACTTCTTCGAGTACAAGAAGAGCCG  
CAGTGGGAGGCACGTCGTCTTCTACCCAACCCTGAAGTCCCTGCAGGTGC  
GGCTGGAGCTGGCCCGGGAGCTGGGCGTTGGGGTCTCTATCTGGGAGCTG  
GGCCAGGGCCTGGACTACTTCTACGACCTGCTCTAGGTGGGCATTGCGGC  
30 CTCCGCGGTGGACGTGTTCTTTTCTAAGCCATGGAGTGAGTGAGCAGGTG  
TGAAATACAGGCCTNCACTCCGTTCAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAACTCGAG (SEQ ID NO: 1229),

GGCGTTTTCCGGCCGTGCGTTTGTGGCCGTCCGGCCTCCCTGACATGCAGC  
CCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCTACCATGCGGAC  
ACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCTGTTCACTAC  
CCTGTCAAAGTCAGATGCCAAAAAGCCGCCTCAAAGACGCTGCTGGAGA  
5 AGAGTCAGTTTTTCAGATAAGCCGGTGCAAGACCGGGGTTTGGTGGTGACG  
GACCTCAAAGCTGAGAGTGTGGTTCTTGAGCATCGCAGCT<sub>a</sub>CTGCT<sub>c</sub>GGCA  
AAGGCCCGGGACAGACACTTTGCTGGGGATGTACTGGGCTATGTCACTCC  
ATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTGGGAGCAAGTTCA  
CACAGATCTCACCCGTCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGATG  
10 TTTGAGGTACGGGCCTCCACGACGTGGACCAAGGGTGGATGCGAGCTGT  
CAGGAAGCATGCCAAGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGG  
ACTGGACTTACGATGATTTCCGGAACGTCTTAGACAGTGAGGATGAGATA  
GAGGAGCTGAGCAAGACCGTGGTCCAGGTGGCAAAGAACCAGCATTTCG  
ATGGCTTCGTGGTGGAGGTCTGGAACCAGCTGCTAAGCCAGAAGCGCGTG  
15 GGCCTCATCCACATGCTCACCCACTTGGCCGAGGCTCTGCACCAGGCCCG  
GCTGCTGGCCCTCCTGGTCATCCCGCCTGCCATCACCCCGGGACCGACC  
AGCTGGGCATGTTACGCACAAGGAGTTTGAGCAGCTGGCCCCCGTGCTG  
GATGGT<sub>TT</sub>CAGCCTCATGACCTACGACTACTCTACAGCGCATCAGCCTGG<sub>c</sub>  
CCTAATGCACCC<sub>c</sub>TGTCCTGGGTTCGAGCCTGCGTCCAGGTCCTGGACCCG  
20 AARTYCAAGTGGCGAACAATACTCCTCCTGGGGSTCAACTTCTATGGWATG  
GACTAMGCGACYTCCAANGGATGCCCGTKARCCTGTTGTCGGGGSCAGGT  
AMATYCAGAMACTGAARGACCACANGCCCCGGATGGTGTGGACAGCAA  
GCCTCAAAG (SEQ ID NO:1230), and  
ATAAGAGACAGCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAAC  
25 GCGGNCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCT  
TTCCTGCGTTATCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGT  
GAGCTGATACCGCTCGCCGACGCCGAACGACCGAGCGCAGCGAGTCAGT  
GAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCG  
CGTTGGCCGATTCAATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAA  
30 AGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGG  
CACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTG  
TGAGCGGATAACAATTCACACAGGAAACAGCTATGACCATGATTACGCC

AAGCTCGAAATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCCACCG  
CGGTGGCGGCCGCTCTAGAAGTGGATCCCCCGGGCTGCAGGAATTCG  
GCACGAGGTCCGGCCTCCCTGACATGCAGATTTCCACCCAGAAGACAGAG  
AAGGAGCCAGTGGTCATGGAATGGGCTGGGGTCAAAGACTGGGTGCCTG  
5 GGAGCTGAGGCAGCCACCGTTTCAGCCTGGCCAGCCCTCTGGACCCCGAG  
GTTGGACCCTACTGTGACACACCTACCATGCGGACACTCTTCAACCTCCTC  
TGGCTTGCCCTGGCCTGCAGCCCTGTTACACTACCCTGTCAAAGTCAGAT  
GCCAAAAAAGCCGCCTCAAAGACGCTGCTGGAGAAGAGTCAGTTTTCAGA  
TAAGCCGGTGCAAGACCGGGGTTTGGTGGTGACGGACCTCAAAGCTGAGA  
10 GTGTGGTTCTTGAGCATCGCAGCTACTGCTCGGCAAAGGCCCGGGACAGA  
CACTTTGCTGGGGATGTAAGTGGGCTATGTCACTCCATGGAACAGCCATGG  
CTACGATGTCACCAAGGTCTTTGGGAGCAAGTTCACACAGATCTCACCCG  
TCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGATGTTTGAGGTCACGGGC  
CTCCACGACGTGGACCAAGGGTGGATGCGAGCTGTCAGGAAGCATGCCA  
15 AGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGGACTGGACTTACGAT  
GATTTCCGGAACGTCTTAGACAGTGAGGATGAGATAGAGGAGCTGAGCA  
AGACCGTGGTCCAGGTGGCAAAGAACCAGCATTTCGATGGCTTCGTGGTG  
GAGGTCTGGAACCAGCTGCTAAGCCAGAAGCGCGTGGGCCTCATCCACAT  
GCTCACCCACTTGGCCGAGGCTCTGCACCAGGCCCGGCTGCTGGCCCTCC  
20 TGGTCATCCCGCCTGCCATCACCCCCGGGACCGACCAGCTGGGCATGTTT  
ACGCACAAGGAGTTTGAGCAGCTGGCCCCCGTGCTGGATGGTTTCAGCCT  
CATGACCTACGACTACTCTACAGCGCATCAGCCTGGCCCTAATGCACCCC  
TGTCTTGGGTTTCGAGCCTGCGTCCAGGTCTGGACCCGAAGTCCAAGTGG  
CGAAGCAAAATCCTCCTGGGGCTCAACTTCTATGGTACATCCAGACACTG  
25 AAGGACCACAGGCCCGGATGGTGTGGGACAGCCAGGCCTCAGAGCACT  
TCTTCGAGTACAAGAAGAGCCGCAAGTGGGAGGCACGTCGTCTTCTACCCA  
ACCCTGAAGTCCCTGCAGGTGCGGCTGGAGCTGGCCCGGGAGCTGGGCGT  
TGGGGTCTCTATCTGGGAGCTGGGCCAGGGCCTGGACTACTTCTACGACC  
TGCTCTAGGTGGGCATTGCGGCCTCCGCGGTGGACGTGTTCTTTTCTAAGC  
30 CATGGAGTGAGTGAGCAGGTGTGAAATACAGGCCTCCACTCCGTTAAAAA  
AAAAAAAAAAAAAAAAAACTCGAGGGGGGGCCCGGTACCCAATTCGCCC  
TATAGTGAGTCGTATTACAATTCAGTGGCCGTCGTTTTACAACGTCGTGAC

TGGGAAAACCCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCT  
TTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCA  
ACAGTTGCGCAGCCTGAATGGCGAATGGCAAATTGTAAGCGTTAATATTT  
TGTTAAAATTCGCGTTAAATTTTTGTAAATCAGCTCATTTTTTAACCAAT  
5 AGGCCGAAATCGGCAAAATCCCTTATAAATCAAAGAATAGACCGAGAT  
AGGGTTGAGTGTTGNTCCAGTTTGAACAAGAGTCCACTATTAAAGAACG  
TGGACTCCAACGTCAAAGGGCGAAAAACCGNCTATCAGGGCGATGGCCC  
ACTACGTGAACCATCACCTTAATCAAAGTTTTTTGGGGTCGAGGTNCCCC  
TAAAAGCACTTAATCGGGAACCC (SEQ ID NO:1231). Polypeptides encoded

10 by these polynucleotides are also encompassed by the invention, as are antibodies that bind to these polypeptides.

In other specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MRTLFLNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV  
15 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF  
TQISPVLWLQKRRGREMFVETGLHDVDQGWMRAVRKHAKGLHIVPRLLFED  
WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVGL  
IHMLTHLAEALHQARLLALLVIPAITPGTDQLGMFTHKEFEQLAPVLDGFSL  
MTYDYSTAHPGPNAPLSWVRACVQVLDPKSKWRSKILLGLNFYGTSRH  
20 (SEQ ID NO: 1232),

MRTLFLNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV  
TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF  
TQISPVLWLQKRRGREMFVETGLHDVDQGWMRAVRKHAKGLHIVPRLLFED  
WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVTD  
25 QLGMFTHKEFEQLAPVLDGFSLMTYDYSTAHPGPNAPLSWVRACVQVLDP  
KSKWRSKILLGLNFYGMDYATSKDAREPVVGARYIQLKDHPRMVWDSQ  
XSEHFFEYKKSRSRGRHVVFYPTLQSLQVRLELARELGVGVSIELGQGLDYF  
YDLL (SEQ ID NO: 1233),

MRTLFLNLLWLALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVV  
30 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF  
TQISPVLWLQKRRGREMFVETGLHDVDQGWMRAVRKHAKGLHIVPRLLFED  
WTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVGL

IHMLTHLAEALHQAARLLALLVIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSL  
 MTYDYSTAHPGPNAPLSWVRACVQVLDPKXKWRTKSSWGSTSMXWTRX  
 XPXDARXPVVGXRX (SEQ ID NO: 1234), and

MRTLFLNLLWLALACSPVHTTSLKSDAKKAASKTLLEKSQFSDKPVQDRGLVV  
 5 TDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPWNSHGYDVTKVFGSKF  
 TQISPVWLQLKRRGREMFVETGLHDVDQGWMAVRKHAKGLHIVPRLLFED  
 WTYDDFRNVLDSEDEIBELSKTVVQVAKNQHFDFVVEVWNQLLSQKRVL  
 IHMLTHLAEALHQAARLLALLVIPPAITPGTDQLGMFTHKEFEQLAPVLDGFSL  
 MTYDYSTAHPGPNAPLSWVRACVQVLDPKSKWRSKILLGLNFYGTSRH

- 10 (SEQ ID NO: 1235). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention.
- 15 Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also preferred are polypeptides, comprising or alternatively consisting of, the mature polypeptide which is predicted to consist of residues 23-362 of the foregoing sequence (SEQ ID NO:278), and biologically active fragments of the mature polypeptide (e.g., fragments that inhibit the Mixed Lymphocyte Reaction).  
 20 Polynucleotides encoding these polypeptides are also encompassed by the invention

Figures 1A-B show the nucleotide (SEQ ID NO:40) and deduced amino acid sequence (SEQ ID NO: 278) corresponding to this gene.

- 25 Figure 2 shows an analysis of the amino acid sequence (SEQ ID NO: 278). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the  
 30 highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively

consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 2 are also represented in tabular form in Table 3. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 2, and Table 3: "Res": amino acid residue of SEQ ID NO: 278 and Figures 1A and 1B; "Position": position of the corresponding residue within SEQ ID NO: 278 and Figures 1A and 1B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emmini.

Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 2 and/or Table 3, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 3 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.



Certain preferred regions in these regards are set out in Figure 2, but may, as shown in Table 3, be represented or identified by using tabular representations of the data presented in Figure 2. The DNA\*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 2 in a tabular format (See Table 3). The tabular format of the data in Figure 2 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO:40, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:40. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:40. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to

about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150 from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1400, from  
5 about 1401 to about 1450, and from about 1451 to about 1515, of SEQ ID NO:40, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional  
10 attributes of the corresponding protein.

Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-362 where m is an integer  
15 from 2 to 356, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:278. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: K-23 to L-362; S-24 to L-362; D-25 to L-362; A-26 to L-362; K-27 to L-362; K-28 to L-362; A-29 to L-362; A-30 to L-362;  
20 S-31 to L-362; K-32 to L-362; T-33 to L-362; L-34 to L-362; L-35 to L-362; E-36 to L-362; K-37 to L-362; S-38 to L-362; Q-39 to L-362; F-40 to L-362; S-41 to L-362; D-42 to L-362; K-43 to L-362; P-44 to L-362; V-45 to L-362; Q-46 to L-362; D-47 to L-362; R-48 to L-362; G-49 to L-362; L-50 to L-362; V-51 to L-362; V-52 to L-362; T-53 to L-362; D-54 to L-362; L-55 to L-362; K-56 to L-362; A-57 to L-362; E-58 to  
25 L-362; S-59 to L-362; V-60 to L-362; V-61 to L-362; L-62 to L-362; E-63 to L-362; H-64 to L-362; R-65 to L-362; S-66 to L-362; Y-67 to L-362; C-68 to L-362; S-69 to L-362; A-70 to L-362; K-71 to L-362; A-72 to L-362; R-73 to L-362; D-74 to L-362; R-75 to L-362; H-76 to L-362; F-77 to L-362; A-78 to L-362; G-79 to L-362; D-80 to L-362; V-81 to L-362; L-82 to L-362; G-83 to L-362; Y-84 to L-362; V-85 to L-362;  
30 T-86 to L-362; P-87 to L-362; W-88 to L-362; N-89 to L-362; S-90 to L-362; H-91 to L-362; G-92 to L-362; Y-93 to L-362; D-94 to L-362; V-95 to L-362; T-96 to L-362; K-97 to L-362; V-98 to L-362; F-99 to L-362; G-100 to L-362; S-101 to L-362; K-

102 to L-362; F-103 to L-362; T-104 to L-362; Q-105 to L-362; I-106 to L-362; S-  
107 to L-362; P-108 to L-362; V-109 to L-362; W-110 to L-362; L-111 to L-362; Q-  
112 to L-362; L-113 to L-362; K-114 to L-362; R-115 to L-362; R-116 to L-362; G-  
117 to L-362; R-118 to L-362; E-119 to L-362; M-120 to L-362; F-121 to L-362; E-  
5 122 to L-362; V-123 to L-362; T-124 to L-362; G-125 to L-362; L-126 to L-362; H-  
127 to L-362; D-128 to L-362; V-129 to L-362; D-130 to L-362; Q-131 to L-362; G-  
132 to L-362; W-133 to L-362; M-134 to L-362; R-135 to L-362; A-136 to L-362; V-  
137 to L-362; R-138 to L-362; K-139 to L-362; H-140 to L-362; A-141 to L-362; K-  
142 to L-362; G-143 to L-362; L-144 to L-362; H-145 to L-362; I-146 to L-362; V-  
10 147 to L-362; P-148 to L-362; R-149 to L-362; L-150 to L-362; L-151 to L-362; F-  
152 to L-362; E-153 to L-362; D-154 to L-362; W-155 to L-362; T-156 to L-362; Y-  
157 to L-362; D-158 to L-362; D-159 to L-362; F-160 to L-362; R-161 to L-362; N-  
162 to L-362; V-163 to L-362; L-164 to L-362; D-165 to L-362; S-166 to L-362; E-  
167 to L-362; D-168 to L-362; E-169 to L-362; I-170 to L-362; E-171 to L-362; E-  
15 172 to L-362; L-173 to L-362; S-174 to L-362; K-175 to L-362; T-176 to L-362; V-  
177 to L-362; V-178 to L-362; Q-179 to L-362; V-180 to L-362; A-181 to L-362; K-  
182 to L-362; N-183 to L-362; Q-184 to L-362; H-185 to L-362; F-186 to L-362; D-  
187 to L-362; G-188 to L-362; F-189 to L-362; V-190 to L-362; V-191 to L-362; E-  
192 to L-362; V-193 to L-362; W-194 to L-362; N-195 to L-362; Q-196 to L-362; L-  
20 197 to L-362; L-198 to L-362; S-199 to L-362; Q-200 to L-362; K-201 to L-362; R-  
202 to L-362; V-203 to L-362; T-204 to L-362; D-205 to L-362; Q-206 to L-362; L-  
207 to L-362; G-208 to L-362; M-209 to L-362; F-210 to L-362; T-211 to L-362; H-  
212 to L-362; K-213 to L-362; E-214 to L-362; F-215 to L-362; E-216 to L-362; Q-  
217 to L-362; L-218 to L-362; A-219 to L-362; P-220 to L-362; V-221 to L-362; L-  
25 222 to L-362; D-223 to L-362; G-224 to L-362; F-225 to L-362; S-226 to L-362; L-  
227 to L-362; M-228 to L-362; T-229 to L-362; Y-230 to L-362; D-231 to L-362; Y-  
232 to L-362; S-233 to L-362; T-234 to L-362; A-235 to L-362; H-236 to L-362; Q-  
237 to L-362; P-238 to L-362; G-239 to L-362; P-240 to L-362; N-241 to L-362; A-  
242 to L-362; P-243 to L-362; L-244 to L-362; S-245 to L-362; W-246 to L-362; V-  
30 247 to L-362; R-248 to L-362; A-249 to L-362; C-250 to L-362; V-251 to L-362; Q-  
252 to L-362; V-253 to L-362; L-254 to L-362; D-255 to L-362; P-256 to L-362; K-  
257 to L-362; S-258 to L-362; K-259 to L-362; W-260 to L-362; R-261 to L-362; S-

262 to L-362; K-263 to L-362; I-264 to L-362; L-265 to L-362; L-266 to L-362; G-267 to L-362; L-268 to L-362; N-269 to L-362; F-270 to L-362; Y-271 to L-362; G-272 to L-362; M-273 to L-362; D-274 to L-362; Y-275 to L-362; A-276 to L-362; T-277 to L-362; S-278 to L-362; K-279 to L-362; D-280 to L-362; A-281 to L-362; R-282 to L-362; E-283 to L-362; P-284 to L-362; V-285 to L-362; V-286 to L-362; G-287 to L-362; A-288 to L-362; R-289 to L-362; Y-290 to L-362; I-291 to L-362; Q-292 to L-362; T-293 to L-362; L-294 to L-362; K-295 to L-362; D-296 to L-362; H-297 to L-362; R-298 to L-362; P-299 to L-362; R-300 to L-362; M-301 to L-362; V-302 to L-362; W-303 to L-362; D-304 to L-362; S-305 to L-362; Q-306 to L-362; X-307 to L-362; S-308 to L-362; E-309 to L-362; H-310 to L-362; F-311 to L-362; F-312 to L-362; E-313 to L-362; Y-314 to L-362; K-315 to L-362; K-316 to L-362; S-317 to L-362; R-318 to L-362; S-319 to L-362; G-320 to L-362; R-321 to L-362; H-322 to L-362; V-323 to L-362; V-324 to L-362; F-325 to L-362; Y-326 to L-362; P-327 to L-362; T-328 to L-362; L-329 to L-362; K-330 to L-362; S-331 to L-362; L-332 to L-362; Q-333 to L-362; V-334 to L-362; R-335 to L-362; L-336 to L-362; E-337 to L-362; L-338 to L-362; A-339 to L-362; R-340 to L-362; E-341 to L-362; L-342 to L-362; G-343 to L-362; V-344 to L-362; G-345 to L-362; V-346 to L-362; S-347 to L-362; I-348 to L-362; W-349 to L-362; E-350 to L-362; L-351 to L-362; G-352 to L-362; Q-353 to L-362; G-354 to L-362; L-355 to L-362; D-356 to L-362; and Y-357 to L-362 of SEQ ID NO:278. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: R-2 to H-307; T-3 to H-307; L-4 to H-307; F-5 to H-307; N-6 to H-307; L-7 to H-307; L-8 to H-307; W-9 to H-307; L-10 to H-307; A-11 to H-307; L-12 to H-307; A-13 to H-307; C-14 to H-307; S-15 to H-307; P-16 to H-307; V-17 to H-307; H-18 to H-307; T-19 to H-307; T-20 to H-307; L-21 to H-307; S-22 to H-307; K-23 to H-307; S-24 to H-307; D-25 to H-307; A-26 to H-307; K-27 to H-307; K-28 to H-307; A-29 to H-307; A-30 to H-307; S-31 to H-307; K-32 to H-307; T-33 to H-307; L-34 to H-307; L-35 to H-307; E-36 to H-307; K-37 to H-307; S-38 to H-307; Q-39 to H-307; F-40 to H-307; S-41 to H-307; D-42 to H-307; K-43 to H-307; P-44 to H-307; V-45 to H-307; Q-46 to H-307; D-47 to H-307; R-48 to H-307; G-49 to H-307;

L-50 to H-307; V-51 to H-307; V-52 to H-307; T-53 to H-307; D-54 to H-307; L-55 to H-307; K-56 to H-307; A-57 to H-307; E-58 to H-307; S-59 to H-307; V-60 to H-307; V-61 to H-307; L-62 to H-307; E-63 to H-307; H-64 to H-307; R-65 to H-307; S-66 to H-307; Y-67 to H-307; C-68 to H-307; S-69 to H-307; A-70 to H-307; K-71 to H-307; A-72 to H-307; R-73 to H-307; D-74 to H-307; R-75 to H-307; H-76 to H-307; F-77 to H-307; A-78 to H-307; G-79 to H-307; D-80 to H-307; V-81 to H-307; L-82 to H-307; G-83 to H-307; Y-84 to H-307; V-85 to H-307; T-86 to H-307; P-87 to H-307; W-88 to H-307; N-89 to H-307; S-90 to H-307; H-91 to H-307; G-92 to H-307; Y-93 to H-307; D-94 to H-307; V-95 to H-307; T-96 to H-307; K-97 to H-307; V-98 to H-307; F-99 to H-307; G-100 to H-307; S-101 to H-307; K-102 to H-307; F-103 to H-307; T-104 to H-307; Q-105 to H-307; I-106 to H-307; S-107 to H-307; P-108 to H-307; V-109 to H-307; W-110 to H-307; L-111 to H-307; Q-112 to H-307; L-113 to H-307; K-114 to H-307; R-115 to H-307; R-116 to H-307; G-117 to H-307; R-118 to H-307; E-119 to H-307; M-120 to H-307; F-121 to H-307; E-122 to H-307; V-123 to H-307; T-124 to H-307; G-125 to H-307; L-126 to H-307; H-127 to H-307; D-128 to H-307; V-129 to H-307; D-130 to H-307; Q-131 to H-307; G-132 to H-307; W-133 to H-307; M-134 to H-307; R-135 to H-307; A-136 to H-307; V-137 to H-307; R-138 to H-307; K-139 to H-307; H-140 to H-307; A-141 to H-307; K-142 to H-307; G-143 to H-307; L-144 to H-307; H-145 to H-307; I-146 to H-307; V-147 to H-307; P-148 to H-307; R-149 to H-307; L-150 to H-307; L-151 to H-307; F-152 to H-307; E-153 to H-307; D-154 to H-307; W-155 to H-307; T-156 to H-307; Y-157 to H-307; D-158 to H-307; D-159 to H-307; F-160 to H-307; R-161 to H-307; N-162 to H-307; V-163 to H-307; L-164 to H-307; D-165 to H-307; S-166 to H-307; E-167 to H-307; D-168 to H-307; E-169 to H-307; I-170 to H-307; E-171 to H-307; E-172 to H-307; L-173 to H-307; S-174 to H-307; K-175 to H-307; T-176 to H-307; V-177 to H-307; V-178 to H-307; Q-179 to H-307; V-180 to H-307; A-181 to H-307; K-182 to H-307; N-183 to H-307; Q-184 to H-307; H-185 to H-307; F-186 to H-307; D-187 to H-307; G-188 to H-307; F-189 to H-307; V-190 to H-307; V-191 to H-307; E-192 to H-307; V-193 to H-307; W-194 to H-307; N-195 to H-307; Q-196 to H-307; L-197 to H-307; L-198 to H-307; S-199 to H-307; Q-200 to H-307; K-201 to H-307; R-202 to H-307; V-203 to H-307; G-204 to H-307; L-205 to H-307; I-206 to H-307; H-207 to H-307; M-208 to H-307; L-209 to H-307; T-210 to H-307; H-211 to H-307; L-212 to

H-307; A-213 to H-307; E-214 to H-307; A-215 to H-307; L-216 to H-307; H-217 to H-307; Q-218 to H-307; A-219 to H-307; R-220 to H-307; L-221 to H-307; L-222 to H-307; A-223 to H-307; L-224 to H-307; L-225 to H-307; V-226 to H-307; I-227 to H-307; P-228 to H-307; P-229 to H-307; A-230 to H-307; I-231 to H-307; T-232 to H-307; P-233 to H-307; G-234 to H-307; T-235 to H-307; D-236 to H-307; Q-237 to H-307; L-238 to H-307; G-239 to H-307; M-240 to H-307; F-241 to H-307; T-242 to H-307; H-243 to H-307; K-244 to H-307; E-245 to H-307; F-246 to H-307; E-247 to H-307; Q-248 to H-307; L-249 to H-307; A-250 to H-307; P-251 to H-307; V-252 to H-307; L-253 to H-307; D-254 to H-307; G-255 to H-307; F-256 to H-307; S-257 to H-307; L-258 to H-307; M-259 to H-307; T-260 to H-307; Y-261 to H-307; D-262 to H-307; Y-263 to H-307; S-264 to H-307; T-265 to H-307; A-266 to H-307; H-267 to H-307; Q-268 to H-307; P-269 to H-307; G-270 to H-307; P-271 to H-307; N-272 to H-307; A-273 to H-307; P-274 to H-307; L-275 to H-307; S-276 to H-307; W-277 to H-307; V-278 to H-307; R-279 to H-307; A-280 to H-307; C-281 to H-307; V-282 to H-307; Q-283 to H-307; V-284 to H-307; L-285 to H-307; D-286 to H-307; P-287 to H-307; K-288 to H-307; S-289 to H-307; K-290 to H-307; W-291 to H-307; R-292 to H-307; S-293 to H-307; K-294 to H-307; I-295 to H-307; L-296 to H-307; L-297 to H-307; G-298 to H-307; L-299 to H-307; N-300 to H-307; F-301 to H-307; and Y-302 to H-307 of SEQ ID NO: 1232. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a

large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one  
5 or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 1A-B (SEQ ID NO:278), as described by the general formula 1-n, where n is an integer from 6 to 356, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:278. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or  
10 alternatively consisting of, an amino acid sequence selected from the group: K-23 to L-362; K-23 to L-361; K-23 to D-360; K-23 to Y-359; K-23 to F-358; K-23 to Y-357; K-23 to D-356; K-23 to L-355; K-23 to G-354; K-23 to Q-353; K-23 to G-352; K-23 to L-351; K-23 to E-350; K-23 to W-349; K-23 to I-348; K-23 to S-347; K-23 to V-346; K-23 to G-345; K-23 to V-344; K-23 to G-343; K-23 to L-342; K-23 to E-341;  
15 K-23 to R-340; K-23 to A-339; K-23 to L-338; K-23 to E-337; K-23 to L-336; K-23 to R-335; K-23 to V-334; K-23 to Q-333; K-23 to L-332; K-23 to S-331; K-23 to K-330; K-23 to L-329; K-23 to T-328; K-23 to P-327; K-23 to Y-326; K-23 to F-325; K-23 to V-324; K-23 to V-323; K-23 to H-322; K-23 to R-321; K-23 to G-320; K-23 to S-319; K-23 to R-318; K-23 to S-317; K-23 to K-316; K-23 to K-315; K-23 to Y-314; K-23 to E-313; K-23 to F-312; K-23 to F-311; K-23 to H-310; K-23 to E-309;  
20 K-23 to S-308; K-23 to X-307; K-23 to Q-306; K-23 to S-305; K-23 to D-304; K-23 to W-303; K-23 to V-302; K-23 to M-301; K-23 to R-300; K-23 to P-299; K-23 to R-298; K-23 to H-297; K-23 to D-296; K-23 to K-295; K-23 to L-294; K-23 to T-293; K-23 to Q-292; K-23 to I-291; K-23 to Y-290; K-23 to R-289; K-23 to A-288; K-23 to G-287; K-23 to V-286; K-23 to V-285; K-23 to P-284; K-23 to E-283; K-23 to R-282; K-23 to A-281; K-23 to D-280; K-23 to K-279; K-23 to S-278; K-23 to T-277; K-23 to A-276; K-23 to Y-275; K-23 to D-274; K-23 to M-273; K-23 to G-272; K-23 to Y-271; K-23 to F-270; K-23 to N-269; K-23 to L-268; K-23 to G-267; K-23 to L-266; K-23 to L-265; K-23 to I-264; K-23 to K-263; K-23 to S-262; K-23 to R-261; K-23 to W-260; K-23 to K-259; K-23 to S-258; K-23 to K-257; K-23 to P-256; K-23 to D-255; K-23 to L-254; K-23 to V-253; K-23 to Q-252; K-23 to V-251; K-23 to C-250; K-23 to A-249; K-23 to R-248; K-23 to V-247; K-23 to W-246; K-23 to S-245;

K-23 to L-244; K-23 to P-243; K-23 to A-242; K-23 to N-241; K-23 to P-240; K-23 to G-239; K-23 to P-238; K-23 to Q-237; K-23 to H-236; K-23 to A-235; K-23 to T-234; K-23 to S-233; K-23 to Y-232; K-23 to D-231; K-23 to Y-230; K-23 to T-229; K-23 to M-228; K-23 to L-227; K-23 to S-226; K-23 to F-225; K-23 to G-224; K-23 to D-223; K-23 to L-222; K-23 to V-221; K-23 to P-220; K-23 to A-219; K-23 to L-218; K-23 to Q-217; K-23 to E-216; K-23 to F-215; K-23 to E-214; K-23 to K-213; K-23 to H-212; K-23 to T-211; K-23 to F-210; K-23 to M-209; K-23 to G-208; K-23 to L-207; K-23 to Q-206; K-23 to D-205; K-23 to T-204; K-23 to V-203; K-23 to R-202; K-23 to K-201; K-23 to Q-200; K-23 to S-199; K-23 to L-198; K-23 to L-197; K-23 to Q-196; K-23 to N-195; K-23 to W-194; K-23 to V-193; K-23 to E-192; K-23 to V-191; K-23 to V-190; K-23 to F-189; K-23 to G-188; K-23 to D-187; K-23 to F-186; K-23 to H-185; K-23 to Q-184; K-23 to N-183; K-23 to K-182; K-23 to A-181; K-23 to V-180; K-23 to Q-179; K-23 to V-178; K-23 to V-177; K-23 to T-176; K-23 to K-175; K-23 to S-174; K-23 to L-173; K-23 to E-172; K-23 to E-171; K-23 to I-170; K-23 to E-169; K-23 to D-168; K-23 to E-167; K-23 to S-166; K-23 to D-165; K-23 to L-164; K-23 to V-163; K-23 to N-162; K-23 to R-161; K-23 to F-160; K-23 to D-159; K-23 to D-158; K-23 to Y-157; K-23 to T-156; K-23 to W-155; K-23 to D-154; K-23 to E-153; K-23 to F-152; K-23 to L-151; K-23 to L-150; K-23 to R-149; K-23 to P-148; K-23 to V-147; K-23 to I-146; K-23 to H-145; K-23 to L-144; K-23 to G-143; K-23 to K-142; K-23 to A-141; K-23 to H-140; K-23 to K-139; K-23 to R-138; K-23 to V-137; K-23 to A-136; K-23 to R-135; K-23 to M-134; K-23 to W-133; K-23 to G-132; K-23 to Q-131; K-23 to D-130; K-23 to V-129; K-23 to D-128; K-23 to H-127; K-23 to L-126; K-23 to G-125; K-23 to T-124; K-23 to V-123; K-23 to E-122; K-23 to F-121; K-23 to M-120; K-23 to E-119; K-23 to R-118; K-23 to G-117; K-23 to R-116; K-23 to R-115; K-23 to K-114; K-23 to L-113; K-23 to Q-112; K-23 to L-111; K-23 to W-110; K-23 to V-109; K-23 to P-108; K-23 to S-107; K-23 to I-106; K-23 to Q-105; K-23 to T-104; K-23 to F-103; K-23 to K-102; K-23 to S-101; K-23 to G-100; K-23 to F-99; K-23 to V-98; K-23 to K-97; K-23 to T-96; K-23 to V-95; K-23 to D-94; K-23 to Y-93; K-23 to G-92; K-23 to H-91; K-23 to S-90; K-23 to N-89; K-23 to W-88; K-23 to P-87; K-23 to T-86; K-23 to V-85; K-23 to Y-84; K-23 to G-83; K-23 to L-82; K-23 to V-81; K-23 to D-80; K-23 to G-79; K-23 to A-78; K-23 to F-77; K-23 to H-76; K-23 to R-75; K-23 to D-74; K-23 to R-73; K-23 to A-72;



K-23 to K-71; K-23 to A-70; K-23 to S-69; K-23 to C-68; K-23 to Y-67; K-23 to S-66; K-23 to R-65; K-23 to H-64; K-23 to E-63; K-23 to L-62; K-23 to V-61; K-23 to V-60; K-23 to S-59; K-23 to E-58; K-23 to A-57; K-23 to K-56; K-23 to L-55; K-23 to D-54; K-23 to T-53; K-23 to V-52; K-23 to V-51; K-23 to L-50; K-23 to G-49; K-23 to R-48; K-23 to D-47; K-23 to Q-46; K-23 to V-45; K-23 to P-44; K-23 to K-43; K-23 to D-42; K-23 to S-41; K-23 to F-40; K-23 to Q-39; K-23 to S-38; K-23 to K-37; K-23 to E-36; K-23 to L-35; K-23 to L-34; K-23 to T-33; K-23 to K-32; K-23 to S-31; K-23 to A-30; and K-23 to A-29 of SEQ ID NO:278. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

10        Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: K-23 to R-306; K-23 to S-305; K-23 to T-304; K-23 to G-303; K-23 to Y-302; K-23 to F-301; K-23 to N-300; K-23 to L-299; K-23 to G-298; K-23 to L-297; K-23 to L-296; K-23 to I-295; K-23 to K-294; K-23 to S-293; K-23 to R-292; K-23 to W-291; K-23 to K-290; K-23 to S-289; K-23 to K-288; K-23 to P-287; K-23 to D-286; K-23 to L-285; K-23 to V-284; K-23 to Q-283; K-23 to V-282; K-23 to C-281; K-23 to A-280; K-23 to R-279; K-23 to V-278; K-23 to W-277; K-23 to S-276; K-23 to L-275; K-23 to P-274; K-23 to A-273; K-23 to N-272; K-23 to P-271; K-23 to G-270; K-23 to P-269; K-23 to Q-268; K-23 to H-267; K-23 to A-266; K-23 to T-265; K-23 to S-264; K-23 to Y-263; K-23 to D-262; K-23 to Y-261; K-23 to T-260; K-23 to M-259; K-23 to L-258; K-23 to S-257; K-23 to F-256; K-23 to G-255; K-23 to D-254; K-23 to L-253; K-23 to V-252; K-23 to P-251; K-23 to A-250; K-23 to L-249; K-23 to Q-248; K-23 to E-247; K-23 to F-246; K-23 to E-245; K-23 to K-244; K-23 to H-243; K-23 to T-242; K-23 to F-241; K-23 to M-240; K-23 to G-239; K-23 to L-238; K-23 to Q-237; K-23 to D-236; K-23 to T-235; K-23 to G-234; K-23 to P-233; K-23 to T-232; K-23 to I-231; K-23 to A-230; K-23 to P-229; K-23 to P-228; K-23 to I-227; K-23 to V-226; K-23 to L-225; K-23 to L-224; K-23 to A-223; K-23 to L-222; K-23 to L-221; K-23 to R-220; K-23 to A-219; K-23 to Q-218; K-23 to H-217; K-23 to L-216; K-23 to A-215; K-23 to E-214; K-23 to A-213; K-23 to L-212; K-23 to H-211; K-23 to T-210; K-23 to L-209; K-23 to M-208; K-23 to H-207; K-23 to I-206; K-23 to L-205; K-23 to G-204; K-23 to V-203; K-23 to R-202; K-23 to K-201; K-23 to Q-200; K-23 to S-199; K-23 to L-198; K-23 to L-197; K-23 to Q-196; K-23 to N-

195; K-23 to W-194; K-23 to V-193; K-23 to E-192; K-23 to V-191; K-23 to V-190; K-23 to F-189; K-23 to G-188; K-23 to D-187; K-23 to F-186; K-23 to H-185; K-23 to Q-184; K-23 to N-183; K-23 to K-182; K-23 to A-181; K-23 to V-180; K-23 to Q-179; K-23 to V-178; K-23 to V-177; K-23 to T-176; K-23 to K-175; K-23 to S-174; 5 K-23 to L-173; K-23 to E-172; K-23 to E-171; K-23 to I-170; K-23 to E-169; K-23 to D-168; K-23 to E-167; K-23 to S-166; K-23 to D-165; K-23 to L-164; K-23 to V-163; K-23 to N-162; K-23 to R-161; K-23 to F-160; K-23 to D-159; K-23 to D-158; K-23 to Y-157; K-23 to T-156; K-23 to W-155; K-23 to D-154; K-23 to E-153; K-23 to F-152; K-23 to L-151; K-23 to L-150; K-23 to R-149; K-23 to P-148; K-23 to V-147; 10 K-23 to I-146; K-23 to H-145; K-23 to L-144; K-23 to G-143; K-23 to K-142; K-23 to A-141; K-23 to H-140; K-23 to K-139; K-23 to R-138; K-23 to V-137; K-23 to A-136; K-23 to R-135; K-23 to M-134; K-23 to W-133; K-23 to G-132; K-23 to Q-131; K-23 to D-130; K-23 to V-129; K-23 to D-128; K-23 to H-127; K-23 to L-126; K-23 to G-125; K-23 to T-124; K-23 to V-123; K-23 to E-122; K-23 to F-121; K-23 to M-120; K-23 to E-119; K-23 to R-118; K-23 to G-117; K-23 to R-116; K-23 to R-115; 15 K-23 to K-114; K-23 to L-113; K-23 to Q-112; K-23 to L-111; K-23 to W-110; K-23 to V-109; K-23 to P-108; K-23 to S-107; K-23 to I-106; K-23 to Q-105; K-23 to T-104; K-23 to F-103; K-23 to K-102; K-23 to S-101; K-23 to G-100; K-23 to F-99; K-23 to V-98; K-23 to K-97; K-23 to T-96; K-23 to V-95; K-23 to D-94; K-23 to Y-93; 20 K-23 to G-92; K-23 to H-91; K-23 to S-90; K-23 to N-89; K-23 to W-88; K-23 to P-87; K-23 to T-86; K-23 to V-85; K-23 to Y-84; K-23 to G-83; K-23 to L-82; K-23 to V-81; K-23 to D-80; K-23 to G-79; K-23 to A-78; K-23 to F-77; K-23 to H-76; K-23 to R-75; K-23 to D-74; K-23 to R-73; K-23 to A-72; K-23 to K-71; K-23 to A-70; K-23 to S-69; K-23 to C-68; K-23 to Y-67; K-23 to S-66; K-23 to R-65; K-23 to H-64; 25 K-23 to E-63; K-23 to L-62; K-23 to V-61; K-23 to V-60; K-23 to S-59; K-23 to E-58; K-23 to A-57; K-23 to K-56; K-23 to L-55; K-23 to D-54; K-23 to T-53; K-23 to V-52; K-23 to V-51; K-23 to L-50; K-23 to G-49; K-23 to R-48; K-23 to D-47; K-23 to Q-46; K-23 to V-45; K-23 to P-44; K-23 to K-43; K-23 to D-42; K-23 to S-41; K-23 to F-40; K-23 to Q-39; K-23 to S-38; K-23 to K-37; K-23 to E-36; K-23 to L-35; 30 K-23 to L-34; K-23 to T-33; K-23 to K-32; K-23 to S-31; K-23 to A-30; and K-23 to A-29 of SEQ ID NO:1232. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described  
5 generally as having residues m-n of SEQ ID NO:278, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a  
10 polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209080, where this portion excludes any integer of amino acid residues from 1 to about 356 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit  
20 No. 209080, or any integer of amino acid residues from 1 to about 356 amino acids from the carboxyl terminus, or any combination of the above amino terminal and carboxyl terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209080. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention have uses, such as, for example, as a marker  
30 in linkage analysis for chromosome 11.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, immune and gastrointestinal disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

When tested against Jurkat cell lines, supernatants removed from cells expressing this gene activated the nuclear-factor kB (NF-kB) transcription factor. Thus, it is likely that this gene activates Jurkat cells by activating a transcriptional factor found within these cells. Nuclear factor kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element were used to screen supernatants for such activity.

Additionally, products of this gene have been found to inhibit the Mixed Lymphocyte Reaction (MLR). This assay is described in Example 58 herein. Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

The tissue distribution in immune cells (e.g., T-cells, macrophages) and inhibition of the MLR indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of many diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus

erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore, polynucleotides and polypeptides of the invention (including fragments, variants, and derivatives) may be also used to treat, prevent and/or diagnose immunological disorders including, but not limited to, arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma.

The tissue distribution in human T-cells and human colon carcinoma indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of immune disorders and gastrointestinal diseases. Non-limiting representative uses for these polynucleotides and polypeptides are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may as be useful as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, in the differentiation and/or proliferation of various cell types (e.g., T, B and natural killer lymphocytes, monocytes, dendritic cells), modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, and/or modulation of cytokine production by accessory cells.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1501 of SEQ ID NO:40, b is an integer of 15 to 1515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 31**

The translation product of this gene shares sequence homology with Ribosomal protein L11 of *Caenorhabditis elegans*. (See Genbank Accession No. 156201.)

20 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
ERGV SINQFCKEFNERTKDIKEGIPLPTKILVKPDRTFEIKIGQPTVSYFLKAAA  
GI EKGARQTGKEVAGLVTLKHVYEIARIKAQDEAFALQDVPLSSVVRSIIG  
SARSLGIRVVKDLSSSEELAAF QKERAIFLAAQKEADLAAQEAAKK (SEQ ID  
25 NO:564), ERGV SINQFCKEFNERTKDIKEGIPLPTKILVKPDRTFEIKIGQ  
PTVSYFL (SEQ ID NO:565), KAAAGIEKGARQTGKEVAGLVTLKHVYEIARIK  
AQDEAFALQDVPLSSV (SEQ ID NO:566), and/or VRSIIGSARSLGIRVVK  
DLSSSEELAAFQKERAIFLAAQKEADLAAQEAAKK (SEQ ID NO:567).

Moreover, fragments and variants of these polypeptides (such as, for example,  
30 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed in human embryo tissue, and to a lesser extent, in human epithelioid sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development disorders and epithelial cell cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the embryonic and epithelial cell systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. embryonic, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 279 as residues: Lys-34 to Gly-40.

The tissue distribution in human embryo indicates that the protein product of this gene is useful for the diagnosis and treatment of developmental disorders and epithelial cancer. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 690 of SEQ ID NO:41, b is an integer of 15 to 704, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

This gene is expressed primarily in resting T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and general immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders of the immune system.



Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:42, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 33

This gene is believed to reside on chromosome 1. Accordingly, polynucleotides derived from this gene are useful in linkage analysis as chromosome 1 markers.

This gene is expressed primarily in prostate, and to a lesser extent in soares adult brain, human umbilical vein endothelial cells, and amniotic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary system and nervous system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, cancerous and wounded tissues) or bodily fluids  
5 (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate indicates that the protein products of this  
10 gene are useful for the diagnosis and treatment of disorders of the urinary and nervous systems. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive  
15 compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1807 of SEQ ID NO:43, b is an integer of 15 to 1821, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene shares sequence homology with R05G6.4 gene product. (See Genbank Accession No. gi|1326338.) This gene also shares sequence homology with the cyclophilin-like protein CyP-60. (See Genbank Accession No. 1199598, see also Biochem. J. 314 (1), 313-319 (1996).)

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- AVYTYHEKKKDTAASGYGTQNIRLSRDAVKDFDCCCLSLQPCHDPVVTDPG  
YLYEREAILEYILHQKKEIARQMKAYEKQRGTRREEQKELQRAASQDHVRGF  
LEKESAIVSRPLNPFTAKALSGTSPDDVQGPSVGPPSKDKDKVLPSFWIPSLT  
10 PEAKATKLEKPSRTVTCMSGKPLRMSDLTPVHFTPLDSSVDRVGLITRSERY  
VCAVTRDSLSNATPCAVLRPSGAVVTLECEVEKLIRKDMVDPVTGDKLTDRDII  
VLQGGT (SEQ ID NO:568),  
YLYEREAILEYILHQKKEIARQMKAYEKQRGTRREEQKELQRAASQDHVRGF  
LE (SEQ ID NO:569),  
15 FTAKALSGTSPDDVQGPSVGPPSKDKDKVLPSFWIPSLTPEAKATKLEKPSR  
TVTCMSGKPL (SEQ ID NO:570),  
VHFTPLDSSVDRVGLITRSERYVCAVTRDSLSNATPCAVLRPSGAVVTLECEVE  
KLI (SEQ ID NO:571), and/or  
MSDLTPVHFTPLDSSVDRVGLITRSERYVCAVTRDSLSNATPCAVLRPSGAVV  
20 TLECEVEKLIRKDM (SEQ ID NO:572).

- Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
25 encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human testis, and to a lesser extent in activated T-cells.

- 30 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

male reproductive disorders and in particular testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the  
5 reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression  
10 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testis indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders of the male reproductive system, and in particular of testicular cancer. Furthermore, this gene is useful for the  
15 treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is  
20 believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone  
25 formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1010 of SEQ ID NO:44, b is an integer of 15 to 1024, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 35

The translation product of this gene shares sequence homology with Lpe5p of *Saccharomyces cerevisiae*, which is thought to be important in the metabolism of phospholipids. The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in liver and brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and nervous systems expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. liver, brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 283 as residues: Pro-14 to Leu-20, Lys-28 to Asn-38, Arg-109 to Arg-114, Lys-119 to Asn-124, Glu-152 to Leu-157, or Pro-172 to Val-180.

The tissue distribution in liver and brain, combined with the homology to Lpe5p of *Saccharomyces cerevisiae* indicates that the protein product of this gene is useful for the diagnosis and treatment of metabolic and nervous disorders.

Additionally, the tissue distribution indicates that the protein product of this gene is  
 5 useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

10 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
 15 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO:45, b is an integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

20

#### *FEATURES OF PROTEIN ENCODED BY GENE NO: 36*

This gene shares sequence homology with the nuclear ribonucleoprotein U  
 25 (HNRNP U), encoded by *C. elegans* (See Genbank Accession gi|1703576.).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MDTSENRPENDVPEPPMPIADQVSNDDEEGSVDEEEKKESLPSFKRKISV  
 VSATKGVPAGNSDTEGGQPGRKRRWGASTATTQKKPSISITTESLKSIPDIKP  
 30 LAGQEAVVDLHADDSETERNGDDGTHDKGLKICRTVTQVVPVPAEGQE  
 NGQREEEEEKEPEAEPPVPPQVSVEVALPPPAEHEVKKVTLGDTLTRRSISQ  
 QKSGVSITIDDPVRTAQVSPPRGKISNIVHISNLVRPFTLGQLKELLGRTGTLV

EEAFWIDKIKSHCFVTYSTVEEAVATRTALHGVKWPQSNPKFLCADYAEQDE  
 LDYHRGLLVDRPSETKTEEQGIPRPLHPPPPPVQPPQHPRAEQREQERAVRE  
 QWAEREREMERRERTRSEREWDRDKVREGPRSRSRSRXRRRKERAKSKEK  
 KSEKKEKAQEEPPAKLLDDLFRKTKAAPCIYWLPLTDSQIVQKEAERAERAK  
 5 EREKRRKEQEEEEQKEREKEAERERNRQLEREKRREHSRERDRERERERERD  
 RGD RDRDRERDRERGRERDRRDTKRHSRSRSRSTPVRDRGGR (SEQ ID  
 NO:573),  
 ENDVPEPPMPIADQVSND DRPEGSVEDEEKKESLPSFKRKISVVSA (SEQ ID  
 NO:574), VDLHADD SRISED ETERN GDDGTHDKGLKICRTVTQV (SEQ ID  
 10 NO:575),  
 PQVSVEVALPPPAEHEVKKVTLGDTLTRRSISQQKSGVSITIDDPVRTAQVPSP  
 P (SEQ ID NO:576),  
 LKELLGRTGTLVEEAFWIDKIKSHCFVTYSTVEEAVATRTALHGVKWPQSNP  
 KFL (SEQ ID NO:577),  
 15 VDRPSETKTEEQGIPRPLHPPPPPVQPPQHPRAEQREQERAVREQWAERERE  
 (SEQ ID NO:578),  
 EWDRDKVREGPRSRSRSRXRRRKERAKSKEKKSEKKEKAQEEPPAKLLDDL  
 FRKTKAAP (SEQ ID NO:579), LDVPLASRSPEFPLPLMTQSELPRCPPHPGAR  
 (SEQ ID NO:581), LATLSISPIWSVLSL (SEQ ID NO:582), and  
 20 PLTDSQIVQKEAERAERAKEREKRRKEQEEEEQKEREKEAERERNRQLEREK  
 RREHSRERDRER (SEQ ID NO:580). Moreover, fragments and variants of these  
 polypeptides (such as, for example, fragments as described herein, polypeptides at  
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
 25 conditions, to the polynucleotide encoding these polypeptides ) are encompassed by  
 the invention. Antibodies that bind polypeptides of the invention are also  
 encompassed by the invention. Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

An additional embodiment is the polynucleotides encoding these polypeptides.

30 The gene encoding the disclosed cDNA is thought to reside on chromosome 14.  
 Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 14.

This gene is expressed primarily in epididymus, and to a lesser extent in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the male reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. epididymus, testes, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in epididymus and testes indicates that the protein product of this gene is useful for the diagnosis and treatment of male reproductive disorders. Furthermore, the protein product of this gene is useful for the treatment and diagnosis of conditions concerning proper reproductive and testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 37



This gene is expressed primarily in amygdala.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory diseases and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the amygdala, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in amygdala indicates that the protein product of this gene is useful for the diagnosis and treatment of inflammatory diseases and neural disorders. The amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 826 of SEQ ID NO:47, b is an integer of 15 to 840, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

This gene shares sequence homology with human opsonin protein P35  
 5 fragment. (See Genbank Accession No. R94181.) The opsonin protein activates the  
 phagocytosis of pathogenic microbes by phagocytic cells which indicates that the  
 protein product of this gene may be useful in the treatment and/or prevention of a  
 variety of immune conditions, particularly bacterial infections and antigen  
 presentation.

10 In specific embodiments, polypeptides of the invention comprise, or  
 alternatively consists of, an amino acid sequence selected from the group:  
 GCDSCPPHLPREAFAQDTQAEGECSSRAERADMCPDAPPSQEVPEGPGAAP  
 (SEQ ID NO:583),  
 RGWLPSSCLSCALRVCPDSSSTQAMGMLLAFWLPGASWQEAARGQYSEDED  
 15 TDTDEYKEAKASINPVTGRVEEKPPNPMEGMTEEQKEHEA (SEQ ID NO:584),  
 and/or TQAMGMLLAFWLPGASWQEAARGQYSE (SEQ ID NO:585). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 20 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

This gene is expressed in immune-related tissues such as thymus, macrophage,  
 25 and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 immune disorders and infectious diseases. Similarly, polypeptides and antibodies  
 30 directed to these polypeptides are useful in providing immunological probes for  
 differential identification of the tissue(s) or cell type(s). For a number of disorders of  
 the above tissues or cells, particularly of the immune system, expression of this gene

at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative  
5 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 286 as residues: Lys-9 to Arg-14, or Met-38 to Asp-51.

The tissue distribution in immune tissues, particularly macrophages, combined  
10 with the homology to a conserved human opsonin protein indicates that the protein product of this gene is useful for diagnosis and treatment of immune disorders, as well as the treatment and/or diagnosis of infectious disease. Moreover, the gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of  
15 cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne,  
20 neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's  
25 disease; scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
 5 formula of a-b, where a is any integer between 1 to 2418 of SEQ ID NO:48, b is an integer of 15 to 2432, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 39

The translation product of this gene shares sequence homology with alpha-2 type I collagen which is thought to be important in tissue repair. (See, e.g., Genbank Accession No. 211607.)

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 PQLPSCGRPWPGTASVFQSHTQGPREDPDPCRAQGSAGTHCPISLSPPRQ (SEQ ID NO:586),  
 KTHPRALWSAGPSCALCPGGSGXTSPPQGAPRGIXWDRCPQIQVLEGQRVRF  
 20 PSQPQHPSHLAPRGGCGWRPDSRPLLTPSGLSSFFPLDA QCWPWRTVSWR (SEQ ID NO:587),  
 AGAPGQQARLQYLLSFQGE GAPHEXGATGEGGDGAWEACXCXRCLLNWQA  
 GGWGLQLSLMWLHRGPLRPPGVRWTPWAFLEACSWGPALSLLGSGHSLPGT  
 HEQAAWSRGCQHGSPTQKCKSSKEPLAQAPPWDSPAAPPHQGFADVLER  
 25 PTLEPFGVLAPPVPSALVEAAXQVLLREPQGGFXGTAAHRSRCWKGSG (SEQ ID NO:588),  
 MQLLFLLPHSPQLHASLPHSAALPCPRGESLTTASPAGAAGR XDAVPRCRH  
 QAGRGWVPRGPCERGGGDRGKPRAVAWDXGSLRWAVWSARAGQGRSSEP  
 APLASRRGYSTCCLSRGKGLPMRXGRRGRGVMVPGKPACAXGAC (SEQ ID  
 30 NO:589), QHPSHLAPRGGCGWRPDSRPLLTPSGLSSFFPL (SEQ ID NO:590),  
 GVRWTPWAFLEACSWGPALSLLGSGHSLPG (SEQ ID NO:591),  
 WDSAAPPHQGFADVLERPTLEPFGVLA (SEQ ID NO:592), and/or

RSSEPAPLASRRGYSTCCLSRGKGL PMR (SEQ ID NO:593). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the brain, and to a lesser extent, in the kidney and thymus

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain, kidney, endocrine, hematopoietic, and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, kidney, and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, urogenital, renal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and thymus, combined with the homology to an alpha-2 type I collagen protein indicates that the protein product of this gene is useful for the diagnosis and treatment of tissue repair, and brain, kidney, immune disorders. Moreover, this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1728 of SEQ ID NO:49, b is an integer of 15 to 1742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 40**

The translation product of this gene shares sequence homology with mini-collagen which is thought to be important in tissue repair and tumor metastasis, and  
20 potentially in cellular migration, attachment, and/or chemotaxis. (See Genbank Accession No. gnl|PID|d1006976.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

PGFRGPSGLGCSFFPRSLGRVLPPGCQRPGAHADSSPPPTP (SEQ ID NO:594).

25 Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind  
30 polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

5 This gene is expressed in ovarian cancer, and to a lesser extent, in dendritic cells and smooth muscle.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumor metastasis, tissue repair, integumentary, reproductive, and/or immune disorders, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor metastasis and tissue repair, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary, immune, hematopoietic, reproductive, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 288 as residues: Asn-2 to His-11.

The tissue distribution in dendritic cells, combined with the homology to the mini-collagen gene indicates that the protein product of this gene is useful for diagnosis and treatment of tumor metastasis and tissue repair. Alternatively, this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1473 of SEQ ID NO:50, b is an integer of 15 to 1487, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 41

This gene shares sequence homology with the HIV TAT protein. (See Genbank Accession No. 328416.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

EDLKKPDPASLRAASC GEGKKRKACKNCTCGLAELEKEKSREQMSSQPKSA  
 CGNCYLGD AFR CASC PYLGMPAFKPGEKVLLS (SEQ ID NO:595);  
 EDLKKPDPASLRAASC GEGKKRKACKNCTCGLAELEKEKSREQMSSQPKSA  
 CGNCYLGD AFR CASC PYLGMPAFKPGEKVLLSDSNLHD (SEQ ID NO:596);  
 CGNCYLGD AFR CASC PYLGMPAFKPGEKVLLSDS (SEQ ID NO:597);  
 SCGEGKKRKACKNCTCGLAELEKE (SEQ ID NO:598),  
 SQPKSACGNCYLGD AFR CASC (SEQ ID NO:599); CCCVSKDQGIMGPGFR  
 (SEQ ID NO:601),  
 HSVTELQTPALSLISAMLPSCSELLVYSILCDTSQVAHNLLRAPEDSLTGCC  
 DDIQCPSAPFHPQPHLTVALHLCPVVYVNLQVLNLLHILTYLEILHVL (SEQ  
 ID NO:602), LLVYSILCDTSQVAHNLLRAPEDS (SEQ ID NO:603),  
 LTVALHLCPVVYVNLQVLNLLHILT (SEQ ID NO:604), and/or  
 REAGQNSERQYVSLSRDP (SEQ ID NO:600). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,



polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are  
5 also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the infant brain, and to a lesser extent, in the breast and testes.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, developmental, reproductive, brain, testes and breast disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).  
15 For a number of disorders of the above tissues or cells, particularly of the brain, testes and breast disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, reproductive, testicular, breast, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, amniotic fluid, lymph, serum, plasma, urine, synovial fluid and  
20 spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 289 as residues: Pro-7 to Val-15.

25 The tissue distribution in infant brain tissue indicates that the protein product of this gene is useful for diagnosis and treatment of neural and other related disorders. Similarly the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's  
30 Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia,

obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular or reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1314 of SEQ ID NO:51, b is an integer of 15 to 1328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 42

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
FFNALYVFRKPQAIFDSEKENKRKNPTKYNNPLRYIYFKVKLIFQFIPLANYKI  
K (SEQ ID NO:605). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the

polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

- 5           The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

          This gene is expressed primarily in the infant brain, human cerebellum, and to a lesser extent, in medulloblastoma.

- 10           Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain related disorders, such as neurodegenerative conditions, medulloblastoma, and other cancers or proliferative conditions. Similarly, polypeptides and antibodies  
15   directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain related disorders and brain cancers, including medulloblastoma, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural,  
20   developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 25           Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 290 as residues: Thr-41 to Glu-47.

- The tissue distribution in infant brain and medulloblastoma indicates that the protein product of this gene is useful for diagnosis and treatment of human brain related disorders, brain cancers, and medulloblastoma. Similarly, the protein product  
30   of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis,

encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1842 of SEQ ID NO:52, b is an integer of 15 to 1856, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 43**

The translation product of this gene shares sequence homology with a phosphotyrosine-independent ligand for the lck SH2 domain which is thought to be important in signal transduction related to phosphotyrosine-independent ligand for the lck SH2 domain, which may implicate this protein as playing an essential role in

30

regulating key cellular processes such as cellular division, and potentially in male fertility. (See Genbank Accession No. gi|1184951.)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 5 ESSGQARTLADPGPGWPRQQGMCFGSLTGLSTTPHGFLTVSAEADPRLIESLS  
QMLSMGFSDEGGWLTRLLQTKNYDIGAALDTIQYSKH (SEQ ID NO:606),  
YSMVYTYHIFFIHSLLDGQLGWFHIFAIVSCAAPDIIFNSFAFSTYISKSCSFYLQ  
NVSCIHSSLSIFNLFQCPIISCMEECNNWLTGLFLHFKIKRCDR (SEQ ID  
NO:607),
- 10 LSPSPRCCPWASLMKAAGSPGSCRPTMTSERLWTPSSIQSIPRRCDHFCPPLL  
RAPLLSHSCVKLA (SEQ ID NO:608),  
GWPRQQGMCFGSLTGLSTTPHGFLTVSAEADPRL (SEQ ID NO:609),  
LGWFHIFAIVSCAAPDIIFNSFAFSTYISKSCS (SEQ ID NO:610),  
SLSIFNLFQCPIISCMEECNNWLTG (SEQ ID NO:611), and/or
- 15 LMKAAGSPGSCRPTMTSERLWTPSSIQSI (SEQ ID NO:612). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
20 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

It is likely that this gene is a new member of a family of phosphotyrosine-independent ligands for the lck SH2 domains.

- 25 This gene is expressed primarily in the placenta, and to a lesser extent, in  
endothelial cells and neutrophils.

- Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
30 reproductive, cardiovascular, immune, and infectious diseases. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the cardiovascular, reproductive, and immune system, and infectious diseases, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cardiovascular, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10           Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 291 as residues: Ile-93 to Arg-98.

          The tissue distribution in placenta and endothelial tissues, combined with the homology to a phosphotyrosine-independent ligand for the lck SH2 domain indicates that the protein product of this gene is useful for diagnosis and treatment of cardiovascular, reproductive, and immune system diseases, as well as infectious diseases. Moreover, the polypeptide of this gene may be able to modulate T or B cell development and/or T or B cell activation (e.g. by modulation of Lck activity). It may also be capable of modulating degradation of cellular proteins (e.g. cell cycle regulatory proteins stimulating expression of cell cycle dependent kinase inhibitors and arresting cell cycle progression at specific boundaries to thereby modulate cell proliferation). p62 acts to boost B cell response and may be used to treat disorders where this is beneficial, e.g. infections by pathogenic microorganisms, e.g. bacteria, viruses and protozoans. p62 can be used to expand T cell populations for treating infectious diseases or cancer, e.g. the resulting cells may be transduced to render them resistant to HIV infection. Inhibitors of p62 can be used to reduce B or T cell responses and may be used to treat a variety of autoimmune diseases, e.g. diabetes mellitus, arthritis, multiple sclerosis allergic reactions, Crohn's diseases etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1544 of SEQ ID NO:53, b is an integer of 15 to 1558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequences:

15 SSSSPRRPRELLGSLKTPLVRPHSAPLDLPGSFCXHTADPMGALHTRFWGRQT  
WIHRKLRLHGTSRLASKXGIQFLRNPSKTHTPRDAAFRDPGQTPDPQSLQAPS  
PSKCSAPNRATSVWSLKPRLLYKHRPSSDKTPPPGRQAPLLFFSAG (SEQ ID  
NO:613), and/or FLRNPSKTHTPRDAAFRDPGQTPDPQSLQA (SEQ ID NO:614).

Moreover, fragments and variants of these polypeptides (such as, for example,  
20 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
encoding these polypeptides ) are encompassed by the invention. Antibodies that  
bind polypeptides of the invention are also encompassed by the invention.

25 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the fetal brain, cerebellum, and to a lesser extent, in the placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
30 and for diagnosis of diseases and conditions which include, but are not limited to,  
neural, developmental, or reproductive disorders, particularly cancers. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal cell related disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, 5 vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 292 as residues: Thr-20 to Gly-28.

The tissue distribution in fetal brain, combined with the homology to proline-rich protein genes indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal cell related disorders. Similarly, the protein product of this 15 gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, 20 hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in 25 synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Moreover, expression within fetal tissue and other cellular sources marked 30 by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions



involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed  
5 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:54, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide  
15 residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

20 The translation product of this gene shares sequence homology with precerebellin of human, which is thought to be important in synaptic physiology. (See Genbank Accession No. gi|180251.) The cerebellum contains a hexadecapeptide, termed cerebellin, that is conserved in sequence from human to chicken. Three independent, overlapping cDNA genes have been isolated from a  
25 human cerebellum cDNA library that encode the cerebellin sequence. The longest gene codes for a protein of 193 amino acids that we term precerebellin. This protein has a significant similarity (31.3% identity, 52.2% similarity) to the globular (non-collagen-like) region of the B chain of human complement component C1q. The region of relatedness extends over approximately 145 amino acids located in the  
30 carboxyl terminus of both proteins. Unlike C1q B chain, no collagen-like motifs are present in the amino-terminal regions of precerebellin. The amino terminus of precerebellin contains three possible N-linked glycosylation sites. Although

hydrophobic amino acids are clustered at the amino terminus, they do not conform to the classical signal-peptide motif, and no other obvious membrane-spanning domains are predicted from the cDNA sequence. The cDNA predicts that the cerebellin peptide is flanked by Val-Arg and Glu-Pro residues. Therefore, cerebellin is not  
5 liberated from precerebellin by the classical dibasic amino acid proteolytic-cleavage mechanism seen in many neuropeptide precursors. In Northern (RNA) blots, precerebellin transcripts, with four distinct sizes (1.8, 2.3, 2.7, and 3.0 kilobases), are abundant in cerebellum. These transcripts are present at either very low or undetectable levels in other brain areas and extraneural structures. A similar pattern  
10 of cerebellin precursor transcripts are seen in rat, mouse, and human cerebellum. Furthermore, a partial genomic fragment from mouse shows the same bands in Northern blots as the human cDNA gene. During rat development, precerebellin transcripts mirror the level of cerebellin peptide. Low levels of precerebellin mRNA are seen at birth. Levels increase modestly from postpartum day 1 to 8, then increase  
15 more dramatically between day 5 and 15, and eventually reach peak values between day 21 and 56. It has been observed that cerebellin-like immunoreactivity is associated with Purkinje cell postsynaptic structures. Thus, it is likely that this gene also have synaptic activity. Northern analysis showed a brain-specific 2.4kb message. This is consistent with the current insert size we have, suggesting our gene is full-  
20 length and is brain-specific.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
QEGSEPVLLEGECLVVCEPGRAAAGGPGGAALGEAPPGRVAFXAVRSHHHEP  
AGETGNGTSGAIYFDQVLVNEGGGFDRASGSFVAPVRGVYSFRFHVVKVYN  
25 RQTVQVSLMLNTWPVISAFANDPDVTREAAATSSVLLPLDPGDRVSLRLRRGX  
STGW (SEQ ID NO:615), GETGNGTSGAIYFDQVLVNEGGGFDRASGSFVAPV  
(SEQ ID NO:616), NDPDVTREAAATSSVLLPLDPGDRVS (SEQ ID NO:617),  
FHVVKVYNRQT (SEQ ID NO:618), IYFDQVLVN (SEQ ID NO:619),  
ESRERSGNRRGAEDRGTCGLQSPSA (SEQ ID NO:620),  
30 EMPQFYFFLKLGLCLAQVPMQRGGIGARGSXXPAXAVXGAREGRRKLSGAGF  
LCLKDLGPSEDEEEARET (SEQ ID NO:621),  
MPQFYFFLKLGLCLAQVPMQRGGIGARG (SEQ ID NO:622),

QATCSASGSPGQFGGCTPSPHGTGSCRHPGQGLRRSQRPQSHRPRSPGPGRS  
 RWPHWCHCRFLLAHGGGFGPQQMPLAQGVPLPGLLPRAPLQQLGQAHPP  
 GTPPPAGRALTTPGPTRPPGPEAPEPRAARDCVGD LVASVAWLPTWLRGSAT  
 HKCPGLLPLFCFRSSPWILTAGTLIVCPL (SEQ ID NO:623),  
 5 GCTPSPHGTGSCRHPGQGLRRSQRP (SEQ ID NO:624),  
 SRWPHWCHCRFLLAHGGGFGPQQMP (SEQ ID NO:625),  
 DCVGD LVASVAWLPTWLRGSATHKCPGL (SEQ ID NO:626),  
 DDRPRVQHQAHLD SLAVVHLHHMEPEAVDTPDRGYEGARGPVKATALVHQ  
 DLVEVDGPTGAIAGFPCWLMVVASDRXKCHSPRGCLSQGCSPGPCCSSSARL  
 10 TDHQALPLQQDGL (SEQ ID NO:627),  
 YEGARGPVKATALVHQDLVEVDGPTGAIAGF (SEQ ID NO:628),  
 MAPLVPLPVSPAGSWWWLRTAXNATRPGGASPRAPPGPAAARPGSQTTR  
 HSPSSRTGSDPSWAHPAPRARSTRTKGSPGLCRGPGSQCG LAPNMAEGLCNP  
 QVPRSSAPLLFPLLSLD SHRRHPDSLPSLGS LNPLSIPVSQLCPASHSYSCCHCS  
 15 S (SEQ ID NO:629), SSRTGSDPSWAHPAPRARSTRTKGSPGLC (SEQ ID  
 NO:630), and/or RRHPDSLPSLGS LNPLSIPVSQLCPAS (SEQ ID NO:631).

Moreover, fragments and variants of these polypeptides (such as, for example,  
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
 20 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in cerebellum and infant brain. By Northern  
 25 analysis, a single transcript of 2.4 kb was observed in brain tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 neural and developmental disorders, particularly neuronal cell signal transduction,  
 30 synaptic physiology, or proliferative conditions such as cancer. Similarly,  
 polypeptides and antibodies directed to these polypeptides are useful in providing  
 immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the neuronal cell signal transduction and synaptic physiology expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in cerebellum and infant brain, combined with the homology to the conserved precerebellin gene or gene family indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal cell related disorders. Furthermore, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:55, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 46

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

STHASGPPAPERLCLPERGTAPWGRRANDAA (SEQ ID NO:632),  
 VRRWWLRTMGAAAHCTPEQRRPRRPATILGMDTQNILHTRLSLCSLSWVSL  
 ASSFXLAXRRKAIVVQQKQSKSKKKKVEKXXLNDSVNENSDTVGQIVHYI  
 MKNEANADV LKAMVADNSLYDPESPVTPSTPGSPVSPGLCHQGGRQGSTS  
 VAIICIRWAVXS RGM CVIGVGTSGGTL (SEQ ID NO:633), and/or  
 IMKNEANADV LKAMVADNSLYDPESPVTP (SEQ ID NO:634). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

This gene is expressed in fetal liver and spleen, and to a lesser extent in bone marrow, umbilical vein, and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system, particularly hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 294 as residues: Asp-30 to Glu-57.

The tissue distribution in fetal liver/spleen and bone marrow indicates that the protein product of this gene is useful for diagnosis and treatment of hematopoietic and immune disorders. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1589 of SEQ ID NO:56, b is an integer of 15 to 1603, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares sequence homology with a 12 kD nucleic acid binding protein of Feline calicivirus which is thought to be important in viral replication and may implicate this protein as playing an integral role in the development of host-viral inhibitors and/or novel vaccines. (See Genbank Accession No. 59264).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

HCHLWASGSCLACFFPGGLTRDAAQQHVTKSYSPPYLSQTSCHSCLVFQPVWL  
PEYTFWNLFMAILQFQMNHSLVLQXGPRHVCRAEEAAAGGPGYSDRAAA  
ARGAPSQWGRPAPKDTLAQTLGQTGRASPRLPAGLGTQAS (SEQ ID NO:635),  
PAPKDTLAQTLGQTGRASPRLPAGLGTQ (SEQ ID NO:636),  
20 TIACFSXKARDMYAEERKRQQLERDQATVTEQLLREGLQASGDAQLRRTRL  
HKLSARREERVQGFLQALELKRADWLARLGTASA (SEQ ID NO:637), and/or  
LRRTRLHKLSARREERVQGFLQALELKR (SEQ ID NO:638). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
25 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention..

30 This gene is expressed primarily in human cardiomyopathy tissue, and to a lesser extent, in T helper cells, fetal brain and synovial sarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular, immune, or developmental disorders, particularly cardiomyopathy which occur secondary to viral infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, neural, developmental, skeletal, immune cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 295 as residues: Trp-20 to Cys-26.

The tissue distribution in cardiomyopathy tissue, combined with the homology to a viral 12 kD nucleic acid binding protein indicates that the protein product of this gene is useful for diagnosis and intervention of cardiomyopathy, including those caused by ischemic, hypertensive, congenital, valvular, or pericardial abnormalities. The gene expression pattern may be the consequence or the cause for these conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:57, b is an



integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 48

The translation product of this gene shares sequence homology with tumor necrosis factor related gene product, which is thought to be important in tumor necrosis, bacterial and viral infection, immune diseases and immunoreactions.

- 10 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:  
 KMNSIPWQIPKITPXLNANLVIVECKPLWFCIGTIKQLKLWNQVFMGFKSMFF  
 RIGKLNLYFTIPYCYLFIDNILGIFYLSILGAQGIKYNFYIQRIFTCLLNLNLKIHSN  
 LA (SEQ ID NO:639), LWFCIGTIKQLKLWNQVFMGFKSMFFR (SEQ ID  
 15 NO:640), YSILGAQGIKYNFYIQRIFTCLLNLN (SEQ ID NO:641), and/or  
 TFKLVRFLE (SEQ ID NO:642). Moreover, fragments and variants of these  
 polypeptides (such as, for example, fragments as described herein, polypeptides at  
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
 20 conditions, to the polynucleotide encoding these polypeptides ) are encompassed by  
 the invention. Antibodies that bind polypeptides of the invention are also  
 encompassed by the invention. Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

- The gene encoding the disclosed cDNA is believed to reside on chromosome  
 25 10. Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 10.

This gene is expressed primarily in colon, and to a lesser extent, in ovarian and breast cancers.

- Polynucleotides and polypeptides of the invention are useful as reagents for  
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 gastrointestinal, reproductive, colon, ovarian, breast disorders, particularly cancers.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, reproductive, colon, ovarian, breast, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon tissue, combined with the homology to tumor necrosis factors indicates that the protein product of this gene is useful for the intervention of cancers of the colon, ovary and breast, particularly because TNF family members are known to be involved in the tumor development. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:58, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 49**

30

The translation product of this gene shares sequence homology with mucins, such as epithelial mucin, which are thought to be important in extracellular matrix

functions such as protection, lubrication and cell adhesion, which are important in a variety of functions, particularly immune chemotaxis and infiltration (See for example Genbank Accession No. R68002).

- In specific embodiments, polypeptides of the invention comprise, or  
 5 alternatively consists of, an amino acid sequence selected from the group:  
 PRSRPALRPGRQRPPSHSATSGVLRPRKKPDP (SEQ ID NO:643),  
 RKSFAKPVLWTNAIQAGRGRVLCYTRPPASSSFSALVPDGNRMEGLRTYFL  
 NAFDPGTDYLYLFPSFTVTFQHCLTVRWAFESLQVPQNRPERWASHPLPTH  
 XPAYLPDNQVXMSASG (SEQ ID NO:644),  
 10 GNRMEGLRTYFLNAFDPGTDYLYLF (SEQ ID NO:645), and/or  
 FQHCLTVRWAFESLQVPQNRPERWASHPLP (SEQ ID NO:646). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 15 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

- Moreover, this gene maps to chromosome 22q11.2-qter, and therefore, can be  
 20 used as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in corpus colosum.

- Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 25 tumors, especially of the corpus colosum, as well as metastatic lesions, autoimmune  
 conditions, and integumentary disorders. Similarly, polypeptides and antibodies  
 directed to these polypeptides are useful in providing immunological probes for  
 differential identification of the tissue(s) or cell type(s). For a number of disorders of  
 the above tissues or cells, particularly of the corpus colosum and other solid tissues,  
 30 expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues or cell types (e.g., integumentary, autoimmune, neural, and  
 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5           The tissue distribution in corpus colosum, combined with the homology to mucins indicates that the protein product of this gene is useful for serum tumor markers or immunotherapy targets because tumor cells have greatly elevated levels of mucin expression and shed the molecules into the epithelial tissues. Moreover, the protein product of this gene is useful for the treatment, diagnosis, and/or prevention of
- 10 various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder,
- 15 psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox,
- 20 molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as
- 25 dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
- 30           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1201 of SEQ ID NO:59, b is an integer of 15 to 1215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 50

This gene is expressed primarily in CD34 depleted buffy coat cord blood and primary dendritic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
15 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders and immunological disorders, particularly those related to developmental or reproductive conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
20 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid,  
25 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 depleted buffy coat cord blood and primary  
30 dendritic cells indicates that the protein product of this gene is useful for the diagnosis and treatment of hematopoietic and immune disorders. Secreted or cell surface proteins in the above tissue distribution often are involved in cell activation (e.g.

cytokines) or molecules involved in cell surface activation. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages.

- 5 The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells  
10 and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly  
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:60, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 51**

- The translation product of this gene shares sequence homology with Interferon induced 1-8 gene encoded polypeptide, which is thought to be important in binding to  
30 retroviral rev responsive elements and may be beneficial in the development of novel inhibitors of host-viral interactions leading to effective viral vaccines.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MTLITPSXKLTFXKGNKSWSSRACSSSTLVDP (SEQ ID NO:647),

FLFLHAVDPWPSNG (SEQ ID NO:648),

5 .WSCQSGVFLVFTGCSVLCQMLSGAVVVWRRSAPEDSAVWQASINKPRGKGR  
HGIKGENTSV (SEQ ID NO:649), and/or LVFTGC

SVLCQMLSGAVVVWRRSAPEDSAVWQASI (SEQ ID NO:650). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in CD34 positive cells and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
viral infection, such as AIDS, and other immune or hematopoietic disorders.

20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
immune system, expression of this gene at significantly higher or lower levels may be  
routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and  
25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum,  
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
from an individual having such a disorder, relative to the standard gene expression  
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 299 as residues: Gln-51 to Trp-62.

The tissue distribution in neutrophils and CD34 positive cells, combined with the homology to interferon induced gene 1-8 indicates that the protein product of this gene is useful for the intervention of retroviral infection including HIV. The factor may be involved in viral stability or viral entry into the cells. Alternatively, the virus/factor complex may elicit the cellular immune reaction and could possibly play a beneficial role in the development of effective inhibitors of host-viral interactions, such as exists for novel viral vaccines. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:61, b is an



integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 52

This gene shares sequence homology to immunoglobulin lambda chain (See Genbank Accession No. 2865484). Therefore it is likely that this gene has activity similar to an immunoglobulin lambda chain and may play a beneficial role in the development of effective immunotherapy-based toxins.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: GHPSPALSIAPSDGSQLPCDEVYPYGEAHVTRYCKKPLTNSHLETEAQSSSL (SEQ ID NO:651),

15 NNKHYSFCGSGFCPVYLGFTGLASHQAVKVLVAVIIPRQDRERICLQAQV GRIHLRGCWTGPPFLDGYWSEAFYNTLSRGPLHRAPHHMATGFHQREQWKE QEKGDQGRHRSLLVASPQKRCYFCCILXVRSESLGPGVEFYXGVNGRR (SEQ ID NO:652), ERICLQAQVGRIHLRGCWTGPPFLDGYWSEAF (SEQ ID NO:653), SDGSQLPCDEVYPYGEAHVTRYCKKPL (SEQ ID NO:654), and/or

20 HQREQWKEQEKGDQGRHRSLLVASPQK (SEQ ID NO:655). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these

25 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in Hodgkin's lymphoma.

Polynucleotides and polypeptides of the invention are useful as reagents for

30 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Hodgkin's lymphoma and other immune or hematopoietic disorders. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the

10 disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 300 as residues: Pro-27 to Thr-32.

The tissue distribution in Hodgkin's lymphoma, combined with the sequence homology to immunoglobulin lambda chain protein indicates that the protein product

15 of this gene is useful for the diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an

20 agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:62, b is an

integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 53

This gene has extensive homology to cDNA for Homo sapiens mRNA for the ISLR gene(See Genbank Accession No. AB003184). This protein is considered to be a new member of the Ig superfamily and contains a leucine-rich repeat (LRR) with  
10 conserved flanking sequences and a C2-type immunoglobulin (Ig)-like domain. These domains are important for protein-protein interaction or cell adhesion, and therefore it is possible that the novel protein ISLR may also interact with other proteins or cells. The ISLR gene was mapped on human chromosome 15q23-q24 by fluorescence in situ hybridization (See Medline Article No. 97468140). Homology  
15 to the ISLR gene has been confirmed by another independent group as well (See Genbank Accession No. Hs.102171).

This gene is expressed in a number of tissues including human retina, heart, skeletal muscle, prostate, ovary, small intestine, thyroid, adrenal cortex, testis, stomach, spinal cord, fetal lung and fetal kidney tissues, colon, tonsil and stomach  
20 cancer, and to a lesser extent in endometrial stromal cells treated with estradiol, breast tissue, synovium, lymphoma, and number of other tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
25 tumors of colon, ovary, breast, and integumentary or immune origins. However, due to the wide range of expression in various tissues, protein may play a vital role in the development of cancer in other tissues as well, not just those mentioned above. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
30 type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune,

integumentary, reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, breast milk, seminal fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
5 having the disorder. Additionally, this gene maps to chromosome 15q23-q24, and therefore, can be used as a marker in linkage analysis for chromosome 15.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of  
10 these tumors, in addition to other tumors where expression has been indicated. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell  
15 proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for  
20 treating wounds); stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction, etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for  
25 regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:63, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 54

10

The gene has homology to a multidrug resistance gene 1 (See Genbank Accession No. P06795).

Preferred polynucleotide fragments comprise the following sequence:

gcttcgtgtccaaccctcttgcccttcgcctgtgtgcctggagccagtcaccacgctcgcgtttcctcctgtagtgtcacacaca  
 15 ggtcccagcaccgatggcattcccttgccctgagctctgcagcgggtccctttgtgcttcctcccctcaggtagcctctctc  
 cccctgggccactcccgggggtgaggggttacccttcccagtggttttattcctgtggggctcacccaaagtattaaaa  
 gtagctttgtaa (SEQ ID NO:656),  
 gcttcgtgtccaaccctcttgcccttcgcctgtgtgcctggagccagtcaccacgctcgcgtttcctcctgtagtgtcacacaca  
 ggtcccagcaccgatggcattcccttgccctgagctctgcagcgggtccctttgtgcttcctcccctcaggtagcctctctc  
 20 cccctgggccactcccgggggtgaggggttacccttcccagtggttttattcctgtggggctcacccaaagtattaaaa  
 gtagctttgtaa (SEQ ID NO:657),  
 gcttcgtgtccaaccctcttgcccttcgcctgtgtgcctggagccagtcaccacgctcgcgtttcctcctgtagtgtcacacaca  
 ggtcccagcaccgatggcattcccttgccctgagctctgcagcgggtccctttgtgcttcctcccctcaggtagcctctctc  
 cccctgggccactcccgggggtgaggggttacccttcccagtggttttattcctgtggggctcacccaaagtattaaaa  
 25 gtagctttgtaa (SEQ ID NO:658). Also preferred are polypeptides comprising one or  
 more of the fragments encoded by these polynucleotide fragments.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

FRINRLTIGXAVAMTRGNQRELARQKNMKKQSDSVKGKRRDDGLSAAARK  
 30 QRDSEI (SEQ ID NO:659), AVAMTRGNQRELARQKNMKKQSDSVKGKR (SEQ  
 ID NO:660),  
 KSRATRLRESAEMTGFLPPASRGTRRSCSRSRKRQTRRRRNPSFVASCPDLL

PFACVPGASPTTLAFTPVVLTGPSTDGIPFALSQRVPFVLSPQVASLPLGHSR  
G (SEQ ID NO:661), LRESAEMTGFLLPASRGTRRSCSRS (SEQ ID NO:662),  
and/or VVLTGPSTDGIPFALSQRVPFVLSPQVA (SEQ ID NO:663). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
5 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
10 these polypeptides are also encompassed by the invention.

This gene is expressed primarily in lung, esophagus, leukemia (Jurkat cells),  
breast cancers and to a lesser extent, in macrophages treated with GM-CSF fetal  
tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for  
15 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
immune, developmental, or pulmonary disorders, particularly cancers. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
immunological probes for differential identification of the tissue(s) or cell type(s).  
20 For a number of disorders of the above tissues or cells, particularly of the solid  
tumors, lung and leukemia, expression of this gene at significantly higher or lower  
levels may be routinely detected in certain tissues or cell types (e.g., immune,  
developmental, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g.,  
lymph, pulmonary surfactant and sputum, amniotic fluid, serum, plasma, urine,  
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder. Furthermore, due to the high expression level in lung tissue and the  
proposed function of the multidrug resistance protein 1 gene as the efflux pump  
30 responsible for low-drug accumulation in multidrug-resistant cells, protein as well  
mutants thereof, may also be beneficial as a target for gene therapy, particularly for  
the chronic patient.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 302 as residues: Met-1 to Lys-16.

The tissue distribution cancers and fetal tissues indicates that the protein product of this gene is useful for the detection of cells in active proliferation, such as  
5 cancers. The gene products may be used for cancer markers or immunotherapy target. Similarly, the secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are  
10 cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for  
15 treating wounds); stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction, etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for  
20 regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 574 of SEQ ID NO:64, b is an

integer of 15 to 588, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 55

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

LLSTSHLLTQSYSFNKRSHSFAWKNAHCILQSENNELQNSVYIYVCIYVHF

10 ICTFLCDI (SEQ ID NO:664), and/or KRSHSFAWKNAHCILQSENNELQNSVYIY  
VCI (SEQ ID NO:665). Moreover, fragments and variants of these polypeptides  
(such as, for example, fragments as described herein, polypeptides at least 80%, 85%,  
90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
15 encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides ) are encompassed by the invention.  
Antibodies that bind polypeptides of the invention are also encompassed by the  
invention. Polynucleotides encoding these polypeptides are also encompassed by the  
invention.

The gene encoding the disclosed cDNA is believed to reside on the X  
20 chromosome. Accordingly, polynucleotides related to this invention are useful as a  
marker in linkage analysis for the X chromosome.

This gene is expressed primarily in the brain, and to a lesser extent, in the  
developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
neurodegenerative disease states and developmental disorders. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
immunological probes for differential identification of the tissue(s) or cell type(s).  
30 For a number of disorders, including X-linked disorders, of the above tissues or cells,  
particularly of the neurological, developmental systems, and cardiovascular system,  
expression of this gene at significantly higher or lower levels may be routinely



detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
5 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neural tissue indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's  
10 Disease, Klinefelter's, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually- or X-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the  
15 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of  
20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 931 of SEQ ID NO:65, b is an  
25 integer of 15 to 945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 56**

30

The translation product of this gene shares sequence homology with paxillin, which is thought to be important in mediating signal transduction from growth factor

receptors to the cytoskeleton. Moreover, in normal hematopoietic cells and myeloid cell lines, tyrosine phosphorylation of paxillin has been shown to be rapidly and transiently induced by interleukin-3 and several other hematopoietic growth factors. The predicted structure of paxillin implicates this molecule in protein-protein  
 5 interactions involved in signal transduction from growth factor receptors and the BCR/ABL oncogene fusion protein to the cytoskeleton.

Preferred polynucleotide fragments comprise the following sequence:

tggtcactgtcttacaatcactgctgtggaatcatgataccacttttagctctttgcatcttccttcagtgtattttgttttcaaga  
 ggaagtagatttaactggacaacttgagtactgacatcattgataataaactggcttggtttcaa (SEQ ID

10 NO:666). Also preferred are polypeptide fragments encoded by these polynucleotide fragments.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

LDELM AHLTEMQAKVAVRADAGKKHLPDKQDHKASLDSMLGGLEQELQDL

15 GIATVPKGHCASCQKPIAGKVIHALGQSWHPEHFVCTHCKEEIGSSPFFERSGL  
 XYCPNDYHQLFSPRCAYCAAPILDKVLTAMNQTWHEHFFCSHCGEVFGAE  
 GFHEKD KKP YCRKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCG  
 DCFTSFSTGSFFELDGRPFCELHYHHRRGTLCHGCGQPITGRCISAMGYKFHP  
 EHFVCAFCLTQLSKGIFREQNDKTYCQPCFNKLF (SEQ ID NO:667),

20 KASLDSMLGGLEQELQDLGIATVPKGHCASCQKPIAGKVIHAL (SEQ ID  
 NO:668),

CPNDYHQLFSPRCAYCAAPILDKVLTAMNQTWHEHFFCSHCGEVFGAEG  
 (SEQ ID NO:669),

DKKP YCRKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSF

25 STGSFFELDGRPFCEL (SEQ ID NO:670),

CGQPITGRCISAMGYKFHPEHFVCAFCLTQLSKGIFREQNDKTYCQ (SEQ ID  
 NO:671),

HKSLAGAXVYTTNIQELNVYSEAQEPKESPPPSKTSAAAQLDELM AHLTEMQ

AKVAVRADAGKKHLPDKQDHKASLDSMLGGLEQELQDLGIATVPKGHCAS

30 CQKPIAGKVIHALGQSWHPEHFVCTHCKEEIGSSPFFERSGLXYCPNDYHQLF  
 SPRCAYCAAPILDKVLTAMNQTWHEHFFCSHCGEVFGAEGFHEKD KKP YC  
 RKDFLAMFSPKCGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSFSTGSFFE

LDGRPFCELYHHRRGTLCHGCGQPITGRCISAMGYKFHPEHFVCAFCFLTQLS  
KGIFREQNDKTYCQPCFNKLFPL (SEQ ID NO:672),

NVYSEAQEPKESPPPSKTSAAA (SEQ ID NO:673),

DSMLGGLEQELQDLGIATVPKGHCAS (SEQ ID NO:674),

5 YLSAMDTVWHPECFVCGDCFTSFSTG (SEQ ID NO:675),

RCISAMGYKFHPEHFVCAFCFLTQLSK (SEQ ID NO:676);

PTRPVLFSTCQSCSSRPVRQEHLGCRTMEELDALLEELERSTLQDSDEYSNP

APLPLDQHRSRKETNLDETSEILSIQDNTSPLPAXSCILPISRSSMSTVKPKSQRN

HHHLLKRQQLLSWMSSWLT (SEQ ID NO:677),

10 PVRQEHLGCRTMEELDALLEELERSTLQ (SEQ ID NO:678),

SCILPISRSSMSTVKPKSQRN (SEQ ID NO:679), WHPEHFVCTHC (SEQ ID  
NO:680), LFSPRC (SEQ ID NO:681), PILDKV (SEQ ID NO:682), TWHPEHFF  
(SEQ ID NO:683), EGFHEKD (SEQ ID NO:684), KFHPEHFVCAFCFL (SEQ ID  
NO:685), PITGRCI (SEQ ID NO:686), and/or HPEHFVC (SEQ ID NO:687).

15 Moreover, fragments and variants of these polypeptides (such as, for example,  
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
encoding these polypeptides ) are encompassed by the invention. Antibodies that  
20 bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
11. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 11.

25 This gene is expressed primarily in brain, and to a lesser extent in the  
developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
30 neurological disease states and developmental abnormalities. Similarly, polypeptides  
and antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain, combined with the homology to the conserved paxillin gene, indicates that the protein product of this gene is useful for the treatment and or detection of disease states associated with abnormal signal transduction in brain and/or the developing embryo. This would include treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects. Moreover, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1852 of SEQ ID NO:66, b is an

integer of 15 to 1866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 57

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

RIYCS EDTFSPXAESGVSWQSSVSQLYQDYE (SEQ ID NO:688). Moreover,  
10 fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of  
15 the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in fetal spleen, brain, and to a lesser extent, in six week old embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for  
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, neurological disorders, and developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
25 type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or  
30 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 305 as residues: Arg-28 to Gly-34.

The tissue distribution in fetal spleen indicates that the protein product of this gene is useful for the treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition the expression of this gene in the early embryo, indicates a key role in embryo development, and hence the gene or gene product could be used in the treatment and or detection of embryonic developmental defects. This would include treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1138 of SEQ ID NO:67, b is an integer of 15 to 1152, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 58**

The translation product of this gene shares sequence homology with the gene disrupted in the neurodegenerative disease dentatorubal-pallidoluytian atrophy. Moreover, the translation product of this gene also shares homology with the

GRASP65 protein, a protein involved in the stacking of Golgi cisternae (See Genbank Accession No. AF015264).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 5 MGSSQSVEIPGGGTEGYHVLRVQENSPGHRAGLEPFFDFIVSINGSRLNKDND  
TLKDLLKXNVEKPVKMLIYSSKTLELRETSVTPSNLWGGQGLLGVSIRFCSFD  
GANENVVHVLEVESNSPAALAGLRPHSDYIIGADTVMNESEDLFSLIETHEAK  
PLKLYVYNTD TDNCREVIITPNSAWGGEGLGCGIGYGYLHRIPTRPFEEGKKI  
SLPGQMAGTPITPLKDGFTFTEVQLSSVNPPSLSPPGTTGIEQSLTGLSISSTPPAVS
- 10 SVLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPAGLPNLPNLPNLP  
PAPHIMPGVGLPELVNPGLPPLPSMPPRNLPGLIAPLPSEFLPSFPLVPESSSAA  
SSGELLSSLPPTSNAPSDPATTTAKADAASSLTVDVTPPTAKAPTTVEDRVGD  
STPVSEKPVSAAVDANASESP (SEQ ID NO:689),  
SVEIPGGGTEGYHVLRVQENSPGHRAGLEPFFDFIVSINGSRLNKDNDTLKDL
- 15 LKXNVEKPVKMLIYSSKTLELRETSVTPSNLWGGQGLLGVSIRFCSFDGANEN  
VWH (SEQ ID NO:690),  
ESNSPAALAGLRPHSDYIIGADTVMNESEDLFSLIETHEAKPLKLYVYNTD TD  
NCREVIITPNSAWGGEGLGCGIGYGYLHRIPTRPFEEGKKISLPGQMAGTPIT  
PLKDGFTFTEVQLSSVNPPSLSPPGTTGIEQSLTGLSISS (SEQ ID NO:691),
- 20 ESNSPAALAGLRPHSDYIIGADTVMNESEDLFSLIETHEAKPLKLYVYNTD TD  
NCREVIITPNSAWGGEGLGCGIGYGYLHRIPTRPFEEGKKISLPGQMAGTPIT  
PLKDGFTFTEVQLSSVNPPSLSPPGTTGIEQSLTGLSISS (SEQ ID NO:692)  
RIPTRPFEEGKKISLPGQMAGTPITPLKDGFTFTEVQLSSVNPPSLSPPGTTGIEQSL  
TGLSISSTPPAVSSVLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPA
- 25 GLPNLPNLPNLPAPHIMPGVGLPELVNPGLPPLPSMPPRN (SEQ ID NO:693),  
PGLPPLPSMPPRNLPGLIAPLPSEFLPSFPLVPESSSAAASSGELLSSLPPTSNAPS  
DPATTTAKADAASSLTVDVTPPTAKAPTTVEDRVGDSTPVSEKPVSAAVDAN  
(SEQ ID NO:694), AWGGEGLGCGIGYGYLHRIPT (SEQ ID NO:695),  
SPAALAGLRP (SEQ ID NO:696), and/or WGGQGLLG (SEQ ID NO:697).
- 30 Moreover, fragments and variants of these polypeptides (such as, for example,  
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the

polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

5       The gene encoding the disclosed cDNA is believed to reside on chromosome

2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in prostate cancer, and to a lesser extent, in the pineal glands and in fetal lung.

10       Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, endocrine, reproductive, pulmonary, developmental disorders.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
15 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous, pulmonary, and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neurological, endocrine, reproductive, pulmonary, developmental, and cancerous and  
20 wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, pulmonary surfactant and sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25       Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 306 as residues: Asn-9 to Leu-14.

The abundance of this gene in the pineal gland and its homology to a gene disrupted in the neurodegenerative disease state Dentatorubral-pallidoluysian atrophy indicates that this gene may be useful in the treatment and/or detection of other  
30 neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Alternatively, the



abundance of this gene in fetal lung would suggest that misregulation of the expression of this protein product in the adult could lead to lymphoma or sarcoma formation, particularly in the lung; that it may also be involved in predisposition to certain pulmonary defects such as pulmonary edema and embolism, bronchitis and  
5 cystic fibrosis; and thus the gene or the gene product encoded by the gene could be used in the detection and/or treatment of these pulmonary disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2469 of SEQ ID NO:68, b is an integer of 15 to 2483, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 59**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
25 RNGALLDKNFFNANSHPVKGERIRRR (SEQ ID NO:698). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are  
30 encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in the developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, proliferating, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene primarily in the embryo indicates the gene plays a key role in embryo development, and that the gene or the protein encoded by the gene could be used in the treatment and or detection of developmental defects in the embryo or in infants. Similarly, the relatively specific expression of this gene product during embryogenesis indicates that it may be a key player in the proliferation, maintenance, and/or differentiation of various cell types during development. It may also act as a morphogen to control cell and tissue type specification. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 522 of SEQ ID NO:69, b is an integer of 15 to 536, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

#### *FEATURES OF PROTEIN ENCODED BY GENE NO: 60*

This gene displays homology to nestin, an intermediate filament protein, the expression of which correlates with the proliferation of central nervous system progenitor cells and is useful in the identification of brain tumors.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

RGSGFGWTSFPRPLPTELTCPGFHRERAFPPDGRVRGVRGWVGIRRGCRVWVG  
 VGACGCSPGSSWRGSAHRASGPADLPVACRXEGGADSPSLPSPP (SEQ ID NO:699), AVWVGACGCSPGSSWRGSAHRA (SEQ ID NO:700), YRP  
 TMEKMKQVVTQTRWMRPDAKRANRRHRRISGKIFAWNPLPKTRFSRLLKAV  
 SENTKRPEPSRPPWMVSHSVEAS (SEQ ID NO:701), and/or  
 FAWNPLPKTRFSRLLKAVSENTKRPEP (SEQ ID NO:702). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in kidney, and to a lesser extent, in brain.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal disorders and neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the excretory and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, urogenital, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
15 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
20 NO: 308 as residues: Thr-130 to Asn-137.

The tissue distribution in brain and kidney, combined with the homology to the conserved nestin protein, indicates that the protein product of this gene is useful for the detection and/or treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease,  
25 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, its abundance in kidney indicates that it is useful in the treatment and detection of acute renal failure and other disease states associated with the kidney, such as nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome,  
30 glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed

against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. .

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 560 of SEQ ID NO:70, b is an integer of 15 to 574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

#### 15    **FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

This gene shares homology with the latrophilin-related protein 1 precursor as well as the calcium-independent alpha-latrotoxin receptor. alpha-Latrotoxin, a black widow spider neurotoxin, can bind to high affinity receptors on the presynaptic plasma membrane and stimulate massive neurotransmitter release in the absence of Ca<sup>2+</sup>. Neurexins, previously isolated as alpha-latrotoxin receptors, require Ca<sup>2+</sup> for their interaction with the toxin and, thus, may not participate in the Ca<sup>2+</sup>-independent alpha-latrotoxin activity. However, latrophilin binds alpha-Latrotoxin with high affinity in the presence of various divalent cations (Ca<sup>2+</sup>, Mg<sup>2+</sup>, Ba<sup>2+</sup>, and Sr<sup>2+</sup>) as well as in EDTA. This presumably membrane-bound protein is localized to and differentially distributed among neuronal tissues, with about four times more latrophilin expressed in the cerebral cortex than in the cerebellum; subcellular fractionation showed that the protein is highly enriched in synaptosomal plasma membranes.

30        In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
IYKVFRHTAGLKPEVSCFENIRSCARXXXXXXXXXXXXXWIFGVLHVHVASV

VTAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNPCC (SEQ ID NO:703),

WIFGVLHVHASVVTAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNPCC (SEQ ID NO:704), IYKVFRHTAGLKPEVSCFENIRSCAR (SEQ ID NO:705),

5 IYKVFRHTAGLKPEVSCFENIRSCARGALALLFLLGTTWIFGVLHVHASVVTAYLFTVSNAFQG (SEQ ID NO:706), and/or

EVSCFENIRSCARGALALLFLLGTTWIFGVLH (SEQ ID NO:707). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 The translation product of this gene also shares sequence homology with CD 97, a seven transmembrane bound receptor (see Genbank Accession No. 2213659). The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

20 This gene is expressed primarily in infant brain and in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, vascular, and hematopoietic disorders. Similarly, polypeptides and  
25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, neural,  
30 hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 309 as residues: Lys-13 to Leu-21.

5           The tissue distribution in infant brain genes suggest that the protein product may be useful in the detection and/or treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder, while its expression in hematopoietic cell  
10       types indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma and immunodeficiency diseases. Moreover, the expression within endothelial tissue indicates that the protein product of this gene may show utility in the treatment and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease,  
15       atherosclerosis, stroke, embolism, and aneurysm. Furthermore, expression within infant tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also  
20       be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25       related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30       formula of a-b, where a is any integer between 1 to 918 of SEQ ID NO:71, b is an integer of 15 to 932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 62**

- 5 In a specific embodiment, polypeptides of the invention, comprise or alternatively consist of, one or more of the following amino acid sequences:  
 TTILRTCTIVCFYYWFNGVMVLLFFLDNRNLLTFNQASIMPFSNTDFLHCLSFK  
 KKLMLLRYIFYVVLGTPTLSLKGDENQIKNLFT (SEQ ID NO:708),  
 IVCFYWFNGVMVLLFFLDNRNLL (SEQ ID NO:709), and/or
- 10 LLRYIFYVVLGTPTLSLKGDENQI (SEQ ID NO:710). Polynucleotides encoding these polypeptides are also encompassed by the invention as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides
- 15 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.
- 20 Also preferred are polypeptides, comprising or alternatively consisting of, the mature polypeptide which is predicted to consist of residues:  
 PTCYSRMRALSQEITRDFNLLQVSEPSEPCVRYLPRLYLDIHNVCVLDKLRDF  
 VASPPCWKVAQVDSLKDKARKLYTIMNSFCRRDLVFLDDCNALEYPIPVTT  
 VLPDRQR (SEQ ID NO:1245) of the foregoing sequence (SEQ ID NO:310), and
- 25 biologically active fragments of the mature polypeptide (e.g., fragments that induce hematopoiesis). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides
- 30 encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are



also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Figures 5A-5B show the nucleotide (SEQ ID NO:72) and deduced amino acid sequence (SEQ ID NO:310) corresponding to this gene.

5        Figure 6 shows an analysis of the amino acid sequence (SEQ ID NO:310). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the  
10        highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 6 are also represented in tabular form in Table 5.  
15        The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 6, and Table 5: "Res": amino acid residue of SEQ ID NO:310 and Figures 5A-5B; "Position": position of the corresponding residue within SEQ ID NO:310 and Figures 5A-5B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions -  
20        Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface  
25        Probability Plot - Emini.

Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet  
30        forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-

forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figures 5A-5B and/or Table 5, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 5 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figures 5A-5B, but may, as shown in Table 5, be represented or identified by using tabular representations of the data presented in Figure 6. The DNA\*STAR computer algorithm used to generate Figure 6 (set on the original default parameters) was used to present the data in Figure 6 in a tabular format (See Table 5). The tabular format of the data in Figure 6 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 72, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:72. By a fragment at least 20 nt in length, for example, is intended fragments

which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:72. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

- 5 Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to  
10 about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, or from about 951 to about 985 of SEQ ID NO:72, or the complementary strand thereto, or the cDNA  
15 contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.
- Preferred polypeptide fragments of the invention comprise, or alternatively consist of,  
20 the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-136 where m is an integer from 2 to 136, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:310. More in particular, the invention provides polynucleotides encoding  
25 polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: R-2 to R-136; T-3 to R-136; P-4 to R-136; G-5 to R-136; P-6 to R-136; L-7 to R-136; P-8 to R-136; V-9 to R-136; L-10 to R-136; L-11 to R-136; L-12 to R-136; L-13 to R-136; L-14 to R-136; A-15 to R-136; G-16 to R-136; A-17 to R-136; P-18 to R-136; A-19 to R-136; A-20 to R-136; R-21 to R-136; P-22 to R-136;  
30 T-23 to R-136; P-24 to R-136; P-25 to R-136; T-26 to R-136; C-27 to R-136; Y-28 to R-136; S-29 to R-136; R-30 to R-136; M-31 to R-136; R-32 to R-136; A-33 to R-136; L-34 to R-136; S-35 to R-136; Q-36 to R-136; E-37 to R-136; I-38 to R-136; T-39 to

R-136; R-40 to R-136; D-41 to R-136; F-42 to R-136; N-43 to R-136; L-44 to R-136; L-45 to R-136; Q-46 to R-136; V-47 to R-136; S-48 to R-136; E-49 to R-136; P-50 to R-136; S-51 to R-136; E-52 to R-136; P-53 to R-136; C-54 to R-136; V-55 to R-136; R-56 to R-136; Y-57 to R-136; L-58 to R-136; P-59 to R-136; R-60 to R-136; L-61 to R-136; Y-62 to R-136; L-63 to R-136; D-64 to R-136; I-65 to R-136; H-66 to R-136; N-67 to R-136; Y-68 to R-136; C-69 to R-136; V-70 to R-136; L-71 to R-136; D-72 to R-136; K-73 to R-136; L-74 to R-136; R-75 to R-136; D-76 to R-136; F-77 to R-136; V-78 to R-136; A-79 to R-136; S-80 to R-136; P-81 to R-136; P-82 to R-136; C-83 to R-136; W-84 to R-136; K-85 to R-136; V-86 to R-136; A-87 to R-136; Q-88 to R-136; V-89 to R-136; D-90 to R-136; S-91 to R-136; L-92 to R-136; K-93 to R-136; D-94 to R-136; K-95 to R-136; A-96 to R-136; R-97 to R-136; K-98 to R-136; L-99 to R-136; Y-100 to R-136; T-101 to R-136; I-102 to R-136; M-103 to R-136; N-104 to R-136; S-105 to R-136; F-106 to R-136; C-107 to R-136; R-108 to R-136; R-109 to R-136; D-110 to R-136; L-111 to R-136; V-112 to R-136; F-113 to R-136; L-114 to R-136; L-115 to R-136; D-116 to R-136; D-117 to R-136; C-118 to R-136; N-119 to R-136; A-120 to R-136; L-121 to R-136; E-122 to R-136; Y-123 to R-136; P-124 to R-136; I-125 to R-136; P-126 to R-136; V-127 to R-136; T-128 to R-136; T-129 to R-136; V-130 to R-136; and L-131 to R-136 of SEQ ID NO:310. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein (e.g., ability to induce hematopoiesis), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptors, ability to activate receptors, ability to bind and block receptor activation, ability to

inhibit receptor activation without binding (e.g., as a dominant negative inhibitor of oligomeric complexes), ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 5A-5B (SEQ ID NO:310), as described by the general formula 1-n, where n is an integer from 6 to 135, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:310. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: M-1 to Q-135; M-1 to R-134; M-1 to D-133; M-1 to P-132; M-1 to L-131; M-1 to V-130; M-1 to T-129; M-1 to T-128; M-1 to V-127; M-1 to P-126; M-1 to I-125; M-1 to P-124; M-1 to Y-123; M-1 to E-122; M-1 to L-121; M-1 to A-120; M-1 to N-119; M-1 to C-118; M-1 to D-117; M-1 to D-116; M-1 to L-115; M-1 to L-114; M-1 to F-113; M-1 to V-112; M-1 to L-111; M-1 to D-110; M-1 to R-109; M-1 to R-108; M-1 to C-107; M-1 to F-106; M-1 to S-105; M-1 to N-104; M-1 to M-103; M-1 to I-102; M-1 to T-101; M-1 to Y-100; M-1 to L-99; M-1 to K-98; M-1 to R-97; M-1 to A-96; M-1 to K-95; M-1 to D-94; M-1 to K-93; M-1 to L-92; M-1 to S-91; M-1 to D-90; M-1 to V-89; M-1 to Q-88; M-1 to A-87; M-1 to V-86; M-1 to K-85; M-1 to W-84; M-1 to C-83; M-1 to P-82; M-1 to P-81; M-1 to S-80; M-1 to A-79; M-1 to V-78; M-1 to F-77; M-1 to D-76; M-1 to R-75; M-1 to L-74; M-1 to K-73; M-1 to D-72; M-1 to L-71; M-1 to V-70; M-1 to C-69; M-1 to Y-68; M-1 to N-67; M-1 to H-66; M-1 to I-65; M-1 to D-64; M-1 to L-63; M-1 to Y-62; M-1 to L-61; M-1 to R-60; M-1 to P-59; M-1 to L-58;

M-1 to Y-57; M-1 to R-56; M-1 to V-55; M-1 to C-54; M-1 to P-53; M-1 to E-52; M-1 to S-51; M-1 to P-50; M-1 to E-49; M-1 to S-48; M-1 to V-47; M-1 to Q-46; M-1 to L-45; M-1 to L-44; M-1 to N-43; M-1 to F-42; M-1 to D-41; M-1 to R-40; M-1 to T-39; M-1 to I-38; M-1 to E-37; M-1 to Q-36; M-1 to S-35; M-1 to L-34; M-1 to A-33; M-1 to R-32; M-1 to M-31; M-1 to R-30; M-1 to S-29; M-1 to Y-28; M-1 to C-27; M-1 to T-26; M-1 to P-25; M-1 to P-24; M-1 to T-23; M-1 to P-22; M-1 to R-21; M-1 to A-20; M-1 to A-19; M-1 to P-18; M-1 to A-17; M-1 to G-16; M-1 to A-15; M-1 to L-14; M-1 to L-13; M-1 to L-12; M-1 to L-11; M-1 to L-10; M-1 to V-9; M-1 to P-8; and M-1 to L-7 of SEQ ID NO:310. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:310, where n and m are integers as described above. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: M-1 to A-15; R-2 to G-16; T-3 to A-17; P-4 to P-18; G-5 to A-19; P-6 to A-20; L-7 to R-21; P-8 to P-22; V-9 to T-23; L-10 to P-24; L-11 to P-25; L-12 to T-26; L-13 to C-27; L-14 to Y-28; A-15 to S-29; G-16 to R-30; A-17 to M-31; P-18 to R-32; A-19 to A-33; A-20 to L-34; R-21 to S-35; P-22 to Q-36; T-23 to E-37; P-24 to I-38; P-25 to T-39; T-26 to R-40; C-27 to D-41; Y-28 to F-42; S-29 to N-43; R-30 to L-44; M-31 to L-45; R-32 to Q-46; A-33 to V-47; L-34 to S-48; S-35 to E-49; Q-36 to P-50; E-37 to S-51; I-38 to E-52; T-39 to P-53; R-40 to C-54; D-41 to V-55; F-42 to R-56; N-43 to Y-57; L-44 to L-58; L-45 to P-59; Q-

46 to R-60; V-47 to L-61; S-48 to Y-62; E-49 to L-63; P-50 to D-64; S-51 to I-65;  
E-52 to H-66; P-53 to N-67; C-54 to Y-68; V-55 to C-69; R-56 to V-70; Y-57 to L-  
71; L-58 to D-72; P-59 to K-73; R-60 to L-74; L-61 to R-75; Y-62 to D-76; L-63 to  
F-77; D-64 to V-78; I-65 to A-79; H-66 to S-80; N-67 to P-81; Y-68 to P-82; C-69  
5 to C-83; V-70 to W-84; L-71 to K-85; D-72 to V-86; K-73 to A-87; L-74 to Q-88;  
R-75 to V-89; D-76 to D-90; F-77 to S-91; V-78 to L-92; A-79 to K-93; S-80 to D-  
94; P-81 to K-95; P-82 to A-96; C-83 to R-97; W-84 to K-98; K-85 to L-99; V-86 to  
Y-100; A-87 to T-101; Q-88 to I-102; V-89 to M-103; D-90 to N-104; S-91 to S-  
105; L-92 to F-106; K-93 to C-107; D-94 to R-108; K-95 to R-109; A-96 to D-110;  
10 R-97 to L-111; K-98 to V-112; L-99 to F-113; Y-100 to L-114; T-101 to L-115; I-  
102 to D-116; M-103 to D-117; N-104 to C-118; S-105 to N-119; F-106 to A-120;  
C-107 to L-121; R-108 to E-122; R-109 to Y-123; D-110 to P-124; L-111 to I-125;  
V-112 to P-126; F-113 to V-127; L-114 to T-128; L-115 to T-129; D-116 to V-130;  
D-117 to L-131; C-118 to P-132; N-119 to D-133; A-120 to R-134; L-121 to Q-135;  
15 and E-122 to R-136 of SEQ ID NO:310. Polynucleotides encoding these  
polypeptides are also encompassed by the invention. Moreover, fragments and  
variants of these polypeptides (such as, for example, fragments as described herein,  
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
these polypeptides and polypeptides encoded by the polynucleotide which  
20 hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides, or the complement thereof are encompassed by the invention.  
Antibodies that bind polypeptides of the invention are also encompassed by the  
invention. Polynucleotides encoding these polypeptides are also encompassed by  
the invention.

25 The present invention is also directed to proteins containing polypeptides at  
least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a  
polypeptide sequence set forth herein as m-n. In preferred embodiments, the  
application is directed to proteins containing polypeptides at least 80%, 85%, 90%,  
95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid  
30 sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 97975 (deposited April 4, 1997) and ATCC Deposit No. 209081 (deposited May 29, 1997), where this portion excludes any integer of  
5 amino acid residues from 1 to about 606 (end of protein minus six) amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 97975 and 209081, or any integer of amino acid residues from 6 to about 612 amino acids from the carboxyl terminus, or any combination of the above amino terminal and carboxyl terminal deletions, of the  
10 complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 97975 and 209081. Polypeptides encoded by these polynucleotides also are encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
15 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis for chromosome 4.

This gene is expressed primarily in fetal liver and fetal spleen.

25 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immunological, developmental, and/or hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
30 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels



may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. For example, polynucleotides and polypeptides of the invention, polynucleotide and polypeptide fragments, and polynucleotide and polypeptide variants, and antibodies directed to these polypeptides are useful for identifying, selecting, targeting and/or stimulating proliferation of hematopoietic stem cells (a.k.a., hematopoietic progenitor cells).

Cytokines typically exert their respective biochemical and physiological effects by binding to specific receptor molecules. Receptor binding then stimulates specific signal transduction pathways (Kishimoto, T., *et al.*, *Cell* 76:253-262 (1994)). The specific interactions of cytokines with their receptors are often the primary regulators of a wide variety of cellular processes including activation, proliferation, and differentiation (Arai, K. -I, *et al.*, *Ann. Rev. Biochem.* 59:783-836 (1990); Paul, W. E. and Seder, R. A., *Cell* 76:241-251 (1994)).

The polynucleotides and polypeptides of this invention may be useful for the diagnosis and treatment of a variety of immune system and hematopoietic disorders, pathologies, and/or deficiencies. For example, this gene and/or gene product may play a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Furthermore, polypeptides of this invention may be involved in the regulation of cytokine production, antigen presentation, or other processes useful for treatment of cancer, particularly leukemia (e.g., by boosting immune responses, suppressing hyperproliferative activity, or enhancing recovery of healthy hematopoietic cell populations during or following chemotherapy). Moreover, the polynucleotides and polypeptides of this invention, as well as antibodies against the polypeptides of this invention, may be useful for treating immunological and hematopoietic disorders; such as for examples, arthritis, asthma, immunodeficiency diseases (e.g. AIDS), leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia,

neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the polypeptide of this invention represents a secreted factor that is likely to have activity in stimulating the differentiation of blood cells, or recruiting immune and hematopoietic cells to sites of injury. Thus, this polypeptide is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 310 as residues: Met-1 to Leu-7, Pro-18 to Cys-27, Ser-29 to Ser-35, Glu-37 to Asp-41, Gln-46 to Cys-54, Asp-72 to Val-78, Pro-81 to Trp-84, Ser-91 to Lys-98, Asn-104 to Leu-111, Asp-116 to Leu-121, and Val-130 to Arg-136. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution of this gene in fetal liver and spleen indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, leukemia, and immunodeficiency diseases. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and

treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as,  
 5 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of  
 10 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 982 of SEQ ID NO:72, b is an  
 15 integer of 15 to 996, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 63

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This gene shares homology with human serum amyloid protein (See Genbank Accession No. W13671).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

25 ALTRIPPGDWVINVTAVSFAGKTTARFFHSSPPSLGDQARTDPGHQRRD (SEQ ID NO:711), SMLLLFPLQERPQQDSFIRLLLAWGTRLELTLDIKGGI (SEQ ID NO:712),  
 TGLWADGFSSHIIPPLMSRVSSSLVPQARRRRMKESCCGLSCKGNSSNIDYPV  
 TGRNSCERAPLCAFALHFQERTXITGXGEDPGPFQXGRVTASRXTLACSHV  
 30 AMTPAGCXQALGTPSSYCVRKAPRA (SEQ ID NO:713), and/or  
 QARRRRMKESCCGLSCKGNSSNIDYPVT (SEQ ID NO:714). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as

described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in fetal liver and spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immune, and/or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in fetal liver-spleen indicates that the gene is important for the treatment or detection of immune or hematopoietic disorders including arthritis, leukemia, and immunodeficiency diseases. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene

product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:73, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 64

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: LWRSSGVER (SEQ ID NO:715). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide

encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome

- 5 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed specifically in the brain.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly neurodegenerative disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 10  
15  
20

- The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal
- 25  
30

differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1055 of SEQ ID NO:74, b is an integer of 15 to 1069, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 65

This gene shares homology with a yeast protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

LQEVNITLPENSVWYERYKFDIPVFHL (SEQ ID NO:716). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention. (See Genbank Accession No. 1332638).

This gene is expressed primarily in fetal tissue (fetus and fetal liver).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic, developmental, immune, and/or hematopoietic disorders, including cancers (e.g. hepatoblastoma). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, developmental, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 313 as residues: Asn-72 to Glu-77.

The tissue distribution in fetal liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed



progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
- 10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 817 of SEQ ID NO:75, b is an integer of 15 to 831, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 66**

- 20 This gene has homology with a B-cell surface antigen which may indicate that this gene plays a role in the immune response, including, but not limited to disorders and infections of the immune system.

- Preferred polynucleotide fragments comprise the following sequence:  
 GTAGCATGTAGCCAGTCGAATAACNTATAAGGACAAAGTGGAGTCCACGC  
 GTGCGCCGTCTAGACTAGTGGATCCCCGGCTGCAGGATTCGGCACGAG  
 25 (SEQ ID NO:718). Also preferred are polypeptides comprising polypeptide fragments encoded by these polynucleotide fragments.

This gene shares homology with an interferon-gamma receptor (See Genbank Accession No.T94535).

- 30 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 MQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGRRFPKTCRAISQNLVFKY  
 KTFCPVRYMQPHRSSLC LHFTSYVFILSTWGSRLTYSTD LKKKKKNSRGGPVP

IRPKS (SEQ ID NO:717),

MQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGRFPKTCRAISQNLVFK  
(SEQ ID NO:719),

PVRYMQPHRSSLCLHFTSYVFILSTWGSLRTYSTDLKKKKKNSRGGPVPIRPK  
5 S (SEQ ID NO:720),

GEEQRDCSLGWRGVGMRATHCQAARMFVLFSLPKYAGL (SEQ ID NO:721),

TSGSPGCRIRHELPGEEQRDCSLGWRGVGMRATHCQAAR (SEQ ID NO:722),

EPPIAKQQECSCFFPFQNMQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGR  
RFPKTCRAISQNLVFKYKTFCPVRYMQPHRSSLCLHFTSYVFILSTWGSLRTY  
10 STDLKKKKKNSRGGPVPIRPKS (SEQ ID NO:723), and/or

QFRACLLCLCFSCPCSPGGPRWNSRQGGRF (SEQ ID NO:724). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide

15 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in T-cells and gall bladder.

20 Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
immunological disorders and conditions (immunodeficiencies, cancer, leukemia,  
hematopoiesis), in addition to metabolic, gastrointestinal, and/or digestive disorders.  
25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
immune and digestive systems, expression of this gene at significantly higher or  
lower levels may be routinely detected in certain tissues or cell types (e.g., immune,  
30 hematopoietic, metabolic, gastrointestinal, digestive, and cancerous and wounded  
tissues) or bodily fluids (e.g., lymph, serum, bile, plasma, urine, synovial fluid and  
spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 314 as residues: Thr-41 to Gly-52.

5       The tissue distribution in T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune disorders, immunosuppressive (transplantation) and immunodeficiencies (e.g. AIDS), inflammation and hematopoietic disorders. Moreover, the expression of this gene in gall bladder would suggest a possible role  
10       for this gene product in digestive disorders, particularly of the pancreas or liver. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
15       related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
20       formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:76, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

## 25       **FEATURES OF PROTEIN ENCODED BY GENE NO: 67**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
NQFTSCILFCDGGHWRELLFQSI       (SEQ       ID       NO:725),  
30       AMSSKLLNLLALLQYSVHDHCHPRLLKRGARATLRHKGWGPSSLRGCESEF  
QIVLIGWGPD LAVGFGRGKLLSRSLPVRHGGVSEFCLPHRDVVRLEKVKK  
(SEQ ID NO:726), and/or GPSSLRGCESEFQIVLIGWGPD LAVGFGRGKLLS (SEQ

ID NO:727). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
5 encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in  
10 linkage analysis for chromosome 11.

This gene is expressed primarily in a variety of fetal and developmental tissues (e.g. fetal spleen, infant brain).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
15 and for diagnosis of diseases and conditions which include, but are not limited to, developmental, immune or neurological abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing immune and  
20 central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a  
25 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 315 as residues: Ser-38 to Ser-43.

The tissue distribution in fetal tissues indicates that the protein product of this  
30 gene is useful for developmental abnormalities or fetal deficiencies. The detection in infant brain would suggest a role in neurological disorders (both developmental and neurodegenerative conditions of the brain and nervous system, behavioral disorders,

depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia). In addition, the detection in spleen would similarly suggest a role in the detection and treatment of immune disorders (e.g.

immunodeficiency, inflammation, cancer, wound healing, tissue repair,  
5 hematopoiesis). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of  
10 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:77, b is an  
15 integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

#### *FEATURES OF PROTEIN ENCODED BY GENE NO: 68*

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In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

TRKNIDFXETEKYYLFSFSNNVSFKNFWLKYN (SEQ ID NO:728). Moreover,

fragments and variants of this polypeptide (such as, for example, fragments as  
25 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this  
30 polypeptide are also encompassed by the invention.

This gene is expressed primarily in spleen, T-cells, and fetal heart.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological or hematopoietic deficiencies or disorders, including AIDS and cardiovascular or developmental conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and cardiovascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, cardiovascular, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen and T-cells indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, autoimmune disorders, immunodeficiencies (e.g. AIDS), immunosuppressive conditions (transplantation) and hematopoietic disorders. Moreover, the expression in fetal heart indicates that the protein product of this gene is useful for the treatment and diagnosis of cardiovascular disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1119 of SEQ ID NO:78, b is an

integer of 15 to 1133, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 69

This gene shares homology with a human collagen protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 10 MPRKTSKCRQLLCSGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPGCXSVPSRGEQSTGSPAAPRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHSKSQGEQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGGVKVAATTEREPEFKI  
KTGKA (SEQ ID NO:729),  
CSGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPGCXSVPSRGEQSTGSPA
- 15 APRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHS (SEQ ID NO:730),  
QGEGQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGGVKVAATTEREPEFKIKTGKA (SEQ ID NO:731),  
IRHEGKRMLNESRKPLSFASRLSSLYFKLGFPCGRSNLYSTCTAAPGGSPGLPLPFYPVADG (SEQ ID NO:732),
- 20 TRAESLFPLLHAFPVFILNSGSLSVVAATFTPPALLLLGAPQASLCLSTQWLTGCLSCLDAPLLSCPSPWLLCPALGLKLAHVSPGVMAAPPGRPLCASRLPHLGAAGEPVLCSPELLGTQLPGXLRGPRLGILPGGRWEEQVLCLAAVSAFLDAPEHRSCRHFEVFLGMCQIT (SEQ ID NO:733),  
PALGLKLAHVSPGVMAAPPGRPLCASRLP (SEQ ID NO:734),
- 25 GGRWEEQVLCLAAVSAFLDAPEHR (SEQ ID NO:735),  
SWPMCPPEWLLLLGGLCVRHVFHTWGQLASPCSVPLGCLAQSCSLGXSVDPDWGFCQGGDGRSRCFAWRLCLHFWTPQSTEVAGTLRSSSACARLHE (SEQ ID NO:736), and/or GDGRSRCFAWRLCLHFWTPQSTEVAGTLR (SEQ ID NO:737). Moreover, fragments and variants of these polypeptides (such as, for
- 30 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal heart.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular or developmental disorders, particularly vascular conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, developmental, skeletal, vascular, and cancerous and wounded tissues) or bodily  
15 fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
20 NO: 317 as residues: Pro-32 to Ser-39.

The tissue distribution in fetal heart indicates that the protein product of this gene is useful for the treatment and diagnosis of cardiovascular disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis), in addition to vascular disorders, such as microvascular disease. Expression within fetal tissue  
25 indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer  
30 therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 647 of SEQ ID NO:79, b is an integer of 15 to 661, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 70

The translation product of this gene shares sequence homology with a chicken single-strand DNA-binding protein. The promoter region of the chicken alpha2(I) collagen gene contains a pyrimidine-rich element that is well conserved in different mammalian species. This sequence can also form an unusual DNA structure as shown by its sensitivity to SI nuclease in vitro and it lies in a region that is DNase I-hypersensitive only when this promoter is active. The high affinity of this protein for this conserved pyrimidine-rich region indicates that it might be involved in the transcriptional regulation of the alpha2(I) collagen gene.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MSPRYPGGPRPPLRIPNQALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQR  
 MTPPRGMVPLGPQNYGGAMRPPLNALGGPGMPGMNMGPGGGRPWPNTN  
 ANSIPYSSASPGNYVGPPGGGGPPGTPIMPSPADSTNSGDNMYTLMNAVPPGP  
 NRPNFPMGPGSDGPMGGLGGMESHMNGSLGSGDMDSISKNSPNNMSLSNQ  
 PGTPRDDGEMGGNFLNPFQSESYSPSMTMSV (SEQ ID NO:738),  
 MSPRYPGGPRPPLRIPNQALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQR  
 MTPPRGMVPLGPQNYGGAMRPPLNALGGPGMPGMNMGPGGGRPWPNTN  
 ANSIPYSSASPGNY (SEQ ID NO:739),

LNALGGPGMPGMNMGPGGGRPWPNPNTNANSIPYSSASPGNYVGPPGGGGPP  
GTPIMPSPADSTNSGDNMYTLMNAVPPGPN (SEQ ID NO:740),  
GPMGGGLGGMESHMNGSLGSGDMDSSISKNSPNNMSLSNQPGTPRDDGEMG  
GNFLNPFQSESYSPSMTMSV (SEQ ID NO:741), TCEHSSEAKAFHDY (SEQ ID  
5 NO:742), and/or RRETCEHSSEAKAFHDYPF (SEQ ID NO:743),. Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
10 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention. (See Genbank Accession  
No. 1562534)

15 This gene is expressed primarily in placenta, and to a lesser extent, in fetal  
heart.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
developmental abnormalities, fetal deficiencies, and particularly of the cardiovascular  
20 system and/or vascular conditions. Similarly, polypeptides and antibodies directed to  
these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the reproductive system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues or cell  
25 types (e.g., developmental, vascular, cardiovascular, reproductive, and cancerous and  
wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine,  
synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
30 disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 318 as residues: Met-1 to Leu-13, Gly-33 to Gly-46, Pro-48 to Gly-57, Pro-63 to

Gly-68, Pro-89 to Asn-102, Ser-108 to Asn-113, Pro-118 to Pro-124, Pro-132 to Asn-141, Pro-151 to Asn-157, Ile-191 to Met-199, Ser-202 to Gly-215, Phe-222 to Pro-229.

The tissue distribution in fetal heart and placenta indicates that the protein product of this gene is useful for the detection and treatment of developmental abnormalities or fetal deficiencies, ovarian and other endometrial cancers, reproductive dysfunction, cardiovascular disorders, and pre-natal disorders, in particular vascular disorders, which include, but are not limited to, stroke, angina, microvascular disease, atherosclerosis, embolism, and aneurysm. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1364 of SEQ ID NO:80, b is an integer of 15 to 1378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 71

25

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: TITLFQSAWCFFSKYCTDFT (SEQ ID NO:744), VRGCEDGGGGGIWGGWWPGQMQMAPWLSCPHRQFPFHSGRQRRQSDLLK EELPQPSGAAGRASGNKPYTPPPASNSLTLRLLSFRFNAFNRSHPQPSLNKYD RQ (SEQ ID NO:745), PWLSCPHRQFPFHSGRQRRQSDLL (SEQ ID NO:746), and/or RLLSFRFNAFNRSHPQPSLN (SEQ ID NO:747). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in fetal liver, and to a lesser extent, in the breast and testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic disorders (including hepatoblastomas), hematopoietic, immune, and/or reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, hepatic, reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). The expression in testes and breast indicates that the protein product of this gene is useful for the

detection and treatment of endocrine and reproductive disorders (e.g. sperm maturation, milk production, testicular and breast cancers). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1426 of SEQ ID NO:81, b is an integer of 15 to 1440, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 72**

In specific embodiments, polypeptides of the invention comprise, or  
20 alternatively consists of, an amino acid sequence selected from the group:  
RDSSLWAAALSFRQQCSSLASCLVSMYSRPGRQHRAKAGAGSQTEQCWGRK  
VDAVV (SEQ ID NO:748), CLVSMYSRPGRQHRAKAGAGSQTEQCW (SEQ ID  
NO:749),  
PEHGFSSCDFWEGAPSSGPKEGGRSPPQLACVWGMNLSSPPCLALLTNRACL  
25 AVNWHRVTLFPGIQVCNQNTGEEKLQDPCPHLSS (SEQ ID NO:750),  
RSPPQLACVWGMNLSSPPCLALLTNRACLA (SEQ ID NO:751),  
CERDSETSSIAMTCIKHKPPKQKKRLSLLPGFRSALPRVCRCHMITVQREAFRT  
HTGCSTSVHLPSRGGFLPDF (SEQ ID NO:752), and/or  
KKRLSLLPGFRSALPRVCRCHMITVQRE (SEQ ID NO:753).

30 Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the

polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5       The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

      This gene is expressed primarily in smooth muscle, and to a lesser extent, in brain.

10       Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular and neurological disorders, particularly embolism, atherosclerosis, stroke, aneurysm, and microvascular disease. Similarly, polypeptides and antibodies  
15       directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, vascular, endothelial,  
20       smooth muscle, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25       The tissue distribution in brain and smooth muscle indicates that the protein product of this gene is useful for the detection and treatment of restenosis, atherosclerosis, stroke, angina, thrombosis, wound healing and other conditions of heart disease. Moreover, the protein product of this gene is useful for the detection and treatment of developmental, degenerative and behavioral conditions of the brain  
30       and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and

sleep disorders). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1367 of SEQ ID NO:82, b is an integer of 15 to 1381, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 73

This gene shares homology with human stromalin-2, which is believed to play an integral role in modulating cellular function of hematopoietic cells and tissues, and may possibly serve as a tumor suppressor.

20 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 QAFVLLSDLLLIFSPQMIVGGRDFLRPLVFFPEATLQSELASFLMDHVFQPGD  
 LGSGA (SEQ ID NO:754),  
 ACSYLLCNPEFTFFSRADFARSQVLDLLTDRFQQELELLQVG (SEQ ID  
 25 NO:755), QKQLSSLRDRMVAFCCLCQSCSLSDVDTEIQEQVST (SEQ ID  
 NO:756), QVILPALTLVYFSILWTLTHISKSDAS (SEQ ID NO:757),  
 STHDLTRWELYEPCCQLLQKAVDTGXVPHQV (SEQ ID NO:758),  
 TSFLFPLQAFVLLSDLLLIFSPQMIVGGRDFLRPLVFFPEATLQSELASFLMDH  
 VFIQ PGDLGSGA (SEQ ID NO:759),  
 30 GWGACSYLLCNPEFTFFSRADFARSQVLDLLTDRFQQELELLQVGAGAGQ  
 WDTPNKGGRGCKTGDVD (SEQ ID NO:760),  
 VWVLDGIMGTEESVSSFFPKPLCPQKQLSSLRDRMVAFCCLCQSCSLSDVDTE

IQEQVSTDSSGSNKASIPAPIPRN (SEQ ID NO:761),  
 NASLPSTSEWLSSSSPSRFYWCLWSWFPLFFSSITFPFLPQSTHDLTRWELYEP  
 CCQLLQKAVDTGXVPHQVSGQARDGLGAGGLXFKDLRSRWPLGVSSLSAW  
 SGQSEEDQVGGGHELLHSSLRRWTLLPGSSWISWKPRILRDSRRRRVN (SEQ  
 5 ID NO:762), VLGEMLLWIFFPSQSSFLDEDEVYNLAATLKRLSAFYK (SEQ ID  
 NO:763), PKPHFSNPLLLQVILPALTLVYFSILWTLTHISKSDASPGECGS (SEQ  
 ID NO:764), and/or HCQFLLG (SEQ ID NO:765). Moreover, fragments and  
 variants of these polypeptides (such as, for example, fragments as described herein,  
 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
 10 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
 under stringent conditions, to the polynucleotide encoding these polypeptides ) are  
 encompassed by the invention. Antibodies that bind polypeptides of the invention are  
 also encompassed by the invention. Polynucleotides encoding these polypeptides are  
 also encompassed by the invention. (See Genbank Accession No.R65208 )

15 The gene encoding the disclosed cDNA is believed to reside on chromosome  
 7. Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 7.

This gene is expressed primarily in the brain (infant brain, adult brain,  
 pituitary, cerebellum, hippocampus, schizophrenic hypothalamus, amygdala).

20 Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 developmental disorders and neurodegenerative diseases of the brain and nervous  
 system, in addition to immune or hematopoietic disorders. Similarly, polypeptides  
 25 and antibodies directed to these polypeptides are useful in providing immunological  
 probes for differential identification of the tissue(s) or cell type(s). For a number of  
 disorders of the above tissues or cells, particularly of the central nervous system,  
 expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues or cell types (e.g., neural, developmental, immune,  
 30 hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
 amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue  
 or cell sample taken from an individual having such a disorder, relative to the



standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 321 as residues: Thr-25 to Lys-36, Lys-55 to Ser-63.

5           The tissue distribution primarily in brain, combined with the homology to the highly conserved SA-1 and SA-2 proteins, indicates that the protein product of this gene is useful for the detection and treatment of developmental, degenerative and behavioral conditions of the brain and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and sleep disorders). Moreover, the protein  
10           product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation,  
15           bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or  
20           proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25           related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30           formula of a-b, where a is any integer between 1 to 1692 of SEQ ID NO:83, b is an integer of 15 to 1706, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 74**

5           In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
EFGTSLVALELHELLYHWETRAQPSLLYVVSDLRWMEFRTSCLLFDFVLFLFLE  
(SEQ ID NO:766),  
TKPGMVGHVPIVPATKXAEAGGSPEPGSSTLQWPMITPCTPSWATEPDHVSE  
10 DE (SEQ ID NO:767), and/or LLYHWETRAQPSLLYVVSDLRWMEFRTSC (SEQ ID NO:768).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
15 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the hypothalamus of a human suffering  
20 from schizophrenia.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the CNS, particularly schizophrenia. Similarly, polypeptides and  
25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, such as schizophrenia expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded  
30 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 322 as residues: Gly-38 to Ala-44.

5           The tissue distribution in the hypothalamus indicates that the protein products of this gene are useful for the study, diagnosis and treatment of schizophrenia and other disorders involving the CNS. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's  
10   Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors,  
15   including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role  
20   in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly  
25   available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
30   more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 559 of SEQ ID NO:84, b is an

integer of 15 to 573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 75

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

LAVSTSFICCADISTALPLGSSRPAPAPRHREHEHGHQARPPRLXTSLMPLST  
 10 PAAAQLLWTQLTPMGGRPGGRHSPPTLHTGPRALPPGPPPSLHVAALSLLR  
 (SEQ ID NO:769),  
 APAVPHQPPGTESTSMGTPGLPGCSXRPLCHYQHQLXPSYFGHSSPPWG  
 AVLVGVTTPHPRCTPAPGPCRLGLHHPCTWQLCLC (SEQ ID NO:770),  
 CADISTALPLGSSRPAPAPRHREHEHGH (SEQ ID NO:771),  
 15 WTQLTPMGGRPGGRHSPPTLHTGPR (SEQ ID NO:772), and/or HQPPGTEST  
 SMGTPGLPGC (SEQ ID NO:773). Moreover, fragments and variants of these  
 polypeptides (such as, for example, fragments as described herein, polypeptides at  
 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
 20 conditions, to the polynucleotide encoding these polypeptides ) are encompassed by  
 the invention. Antibodies that bind polypeptides of the invention are also  
 encompassed by the invention. Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

25 This gene is expressed primarily in endometrial tumors, and to a lesser extent,  
 in amniotic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 reproductive, developmental, and immune disorders, particularly cancers of those  
 30 systems. Similarly, polypeptides and antibodies directed to these polypeptides are  
 useful in providing immunological probes for differential identification of the  
 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and  
5 spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 323 as residues: Ser-3 to Arg-9.

10 The tissue distribution in endometrium and amniotic cells indicates that the protein products of this gene are useful for the study and treatment of developmental, reproductive, and immune disorders, particularly cancers of those systems. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of  
15 cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may  
20 show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 670 of SEQ ID NO:85, b is an  
30 integer of 15 to 684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 76**

In specific embodiments, polypeptides of the invention comprise, or  
 5 alternatively consists of, an amino acid sequence selected from the group:  
 SRGSLPPHLPVRVVRVHRGAKSLKALRQYIGAAHLQLPWDGKDPARPLGI  
 TLCLQMEIQVLG (SEQ ID NO:774),  
 CCSFGFYVMVGSDTAEKQGPIPGSQTEGPWLSRHTHSPRAVPESSTAPAQ  
 PLLLPAPQARRWASNANGWGWDHQREGQANYPYSARPAPHNLHPQYLN  
 10 LHLQTQCYAQSGGWVLPPIG QLKVGOPYILPEGLQGLCSSVHPHNNPVR  
 (SEQ ID NO:775), HRGAKSLKALRQYIGAAHLQLPWDG (SEQ ID NO:776),  
 PAPQARRWASNANGWGWDHQR (SEQ ID NO:777), and/or  
 HPQYLNHLQTQCYAQSGGWVLP (SEQ ID NO:778).

Moreover, fragments and variants of these polypeptides (such as, for example,  
 15 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.  
 20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
 22. Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 22.

This gene is expressed primarily in kidney cortex, and to a lesser extent, in  
 25 early stage human brain.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 renal disorders such as renal cancer, developmental, or neural disorders, particularly  
 30 cancers. Similarly, polypeptides and antibodies directed to these polypeptides are  
 useful in providing immunological probes for differential identification of the  
 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the kidney expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, renal, urogenital, endothelial, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
5 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 324 as residues: Gly-38 to Gly-45, Gly-47 to Gly-52, Pro-92 to Lys-110.

10 The tissue distribution in kidney cortex indicates that the protein products of this gene are useful for the study, treatment and diagnosis of renal diseases, including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms  
15 Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Moreover, the expression within human brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease,  
20 Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in  
25 feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment  
30 and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein product may also show utility in the treatment and/or prevention of a variety

of vascular disorders, particularly embolism, aneurysm, stroke, atherosclerosis, or microvascular disease. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
- 10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1022 of SEQ ID NO:86, b is an integer of 15 to 1036, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 77

- 20 In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:
- TNGIMQYVTFVCVWLILFSIMFLRFIQAVACISTSFLFLAEYYSIIWTYHNSFTYSS  
FVSAVWLL (SEQ ID NO:779), YNFMFNFSKNCQKVFHSGCIITYIPTGNVQGFLF  
FHILALTNT SFXXFCFFIATLVDVKWHLIVLICISLMTNDIILFLCAYGSK
- 25 VFPWRNVPSPLPFQNLVICLLLFSF KKFWP GAV A HL (SEQ ID NO:780),  
CVTQARVQWRDLGSLQPPPGFKRFSCLSLLSRXDYMHLPPR PANFCIFSKM  
GFHHVGQAGLEV LXSSDL PALASQSAXITGEPLRLARIS (SEQ ID NO:781),  
LILFSIMFLRFIQAVACISTSFLF (SEQ ID NO:783), and/or LPPR PANFCIFSK  
MGFHHVGQAGLE (SEQ ID NO:782). Moreover, fragments and variants of these
- 30 polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent



conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5           This gene is expressed primarily in kidney medulla.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic and renal disorders. Similarly, polypeptides and antibodies directed to  
10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, urogenital, endocrine, and cancerous and wounded  
15 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in kidney tissue indicates that the protein products of  
20 this gene are useful for study, treatment and diagnosis of metabolic and renal diseases and disorders. Moreover, this gene or gene product could be used in the treatment and/or detection renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms  
25 Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 894 of SEQ ID NO:87, b is an integer of 15 to 908, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 78

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

ALVPSPQQILPSCFSLMWQVTTKSALVFFKCIYIPFLSAPSLPRLNCLIFCSLD  
VQSQLVFLSSPPVAGVLFFLLSPLGSKSCSTVEX (SEQ ID NO:784), and/or  
15 APSLPRLNCLIFCSLDVQSQLVFLS (SEQ ID NO:785). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these  
20 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in chronic synovitis and microvascular endothelium.

Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal or vascular disorders, such as arthritis and atherosclerosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).  
30 For a number of disorders of the above tissues or cells, particularly of the vascular and skeletal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, synovium,

endothelial cells, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in synovium and microvascular endothelium indicates that the protein products of this gene are useful for study, diagnosis and treatment of arthritic and other inflammatory diseases as well as cardiovascular diseases. Moreover, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). In addition, the protein would also be useful in the treatment and/or prevention of a variety of vascular disorders, which include, but are not limited to, microvascular disease, embolism, thrombosis, aneurysm, stroke, or atherosclerosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 641 of SEQ ID NO:88, b is an integer of 15 to 655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 79**

5           In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: SSPSRVRLRHTPG (SEQ ID NO:786), and/or  
SNTNYCFMFFYFPVKVLVPFKNCYILSLLILPCCICGHQFPRXQACTFCLHTLG  
GFSFSXLFLVLLSFYVQTGFSV (SEQ ID NO:787). Moreover, fragments and  
10       variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are  
15       also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

          This gene is expressed in resting T-cells and activated monocytes.

          Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
20       and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at  
25       significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
30       fluid from an individual not having the disorder.

          The tissue distribution in T-cells and monocytes indicates that the protein products of this gene are useful for the study and treatment of immune diseases such

as inflammatory conditions. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1088 of SEQ ID NO:89, b is an integer of 15 to 1102, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

### 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 80

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

GTSRHGQRPIAPGTPWQREPRVEVMDPAGGPRGVLPRPCRXLVLLNPRGGKG  
KALQLFRSHVQPLLAEEISFTLMLTERRNHARELVRSEELGRWXALVVMXG

5 D GLMHEVVNGLHGAA (SEQ ID NO:788), and/or

RPIAPGTPWQREPRVEVMDPAGGP (SEQ ID NO:789). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
10 under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
15 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

This gene is expressed in a variety of immune system tissues, e.g., neutrophils, T-cells, and TNF induced epithelial and endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infectious and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
25 disorders of the above tissues or cells, particularly of the immune and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
30 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 328 as residues: Met-1 to Trp-6.

The tissue distribution in immune tissues and cells indicates that the protein products of this gene are useful for the study and treatment of infectious diseases, immune and vascular disorders. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1519 of SEQ ID NO:90, b is an integer of 15 to 1533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 81**

5           In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: ASGPLMGXAVLKIFE (SEQ ID NO:790). Polynucleotides encoding these polypeptides are also encompassed by the invention.

          This gene is expressed in activated neutrophils.

10           Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and other immune or hematopoietic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal  
20 fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in neutrophils indicates that the protein products of this gene are useful for the study and treatment of immune disorders. Moreover, this gene  
25 product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including  
30 arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated



cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 561 of SEQ ID NO:91, b is an integer of 15 to 575, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 82

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

LLRSALXSPHLPTVPVLV (SEQ ID NO:791),  
QXRNLAQEAFKWIPQDRPTVRSRXXRMGLSIRLPILASNCCALPFXPTSPLQC  
LWSCHCSFQANTGLAS (SEQ ID NO:792),  
QMTQEPPTSVRAHGIAAWGNGCRDKNTKRLIQYWPESCSGMTKGTGVGRW  
GEXRAERSS (SEQ ID NO:793), and/or HGIAAWGNGCRDKNTKRLIQY (SEQ  
ID NO:794). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,

96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

- 5 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in neutrophils.

- Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,
- 10 inflammatory and other immune or hematopoietic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain
- 15 tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 330 as residues: Ala-83 to Thr-91.

- The tissue distribution in neutrophils indicates that the protein products of this gene are useful for the study and treatment of immune disorders. Moreover, the expression of this gene product in neutrophils indicates a role in the regulation of the
- 25 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene
- 30 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease,

inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue  
5 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may  
10 show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of  
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 625 of SEQ ID NO:92, b is an  
20 integer of 15 to 639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 83

25

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: CERSGYTRMAMDT (SEQ ID NO:795),  
TGSILAVGKKYSLGSYSRGDWHMRVVGLRGLGASTLQGLLIGIKPNKPQGRG  
30 KLQGRSSRKDTVLWPSPEHPHVMVSMAILVYPDLSHYSNPHSTPAALLGCWPP  
FREGEILGLQRPQWPPEERCDRPWLPPC (SEQ ID NO:796),  
GSYSRGDWHMRVVGLRGLGASTLQGLLIG (SEQ ID NO:797), and/or

STPAALLGCWPPFREGEILGLQRPQW (SEQ ID NO:798). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which  
5 hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in human neutrophils.

10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and inflammatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
20 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein products of this  
25 gene are useful for diagnosis and treatment of disorders of the inflammatory and immune systems. Moreover, expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other  
30 processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be

also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 844 of SEQ ID NO:93, b is an integer of 15 to 858, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 84

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

TMGTWVDWLTTNTAHTPAIAAAICAEDFPQRHCGSVERSPDQAC (SEQ ID NO:799), and/or TNTAHTPAIAAAICAEDFPQRHC (SEQ ID NO:800). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as

described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in human neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the inflammatory and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein products of this gene are useful for diagnosis and treatment of disorders of the immune and inflammatory systems. Moreover, the expression of this gene product indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis,

granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:94, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 85

25

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: MSPETKGKGRSFPLK (SEQ ID NO:801),

CQNKCSSETTCGRTRRESNKQARAMAFIFKGKDLFPFVSGDIQPKSSGSMAPD QQGLCYLGSWRSHLYCRLLPMDQVSPALC (SEQ ID NO:802),

KPSPGLAYCSLSWSFHMLFLNICSGITIPVILSSGPSHLSTLSLAVSPRRPGTWV KACSCWCP (SEQ ID NO:803), NKQARAMAFIFKGKDLFPFVSGDI (SEQ ID

NO:804), YLGSWRSHLYCRLLPMDQVSP (SEQ ID NO:805), and/or  
GITIPVILSSGPSHLSTLSLAVSPR (SEQ ID NO:806). Moreover, fragments and  
variants of these polypeptides (such as, for example, fragments as described herein,  
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
5 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
under stringent conditions, to the polynucleotide encoding these polypeptides ) are  
encompassed by the invention. Antibodies that bind polypeptides of the invention are  
also encompassed by the invention. Polynucleotides encoding these polypeptides are  
also encompassed by the invention.

10 This gene is expressed in activated neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
inflammation and immune or hematopoietic diseases. Similarly, polypeptides and  
15 antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of  
disorders of the above tissues or cells, particularly of the immune system and  
inflammatory system, expression of this gene at significantly higher or lower levels  
may be routinely detected in certain tissues or cell types (e.g., immune,  
20 hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
taken from an individual having such a disorder, relative to the standard gene  
expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
individual not having the disorder.

25 The tissue distribution in neutrophils indicates that the protein products of this  
gene are useful for diagnosis and treatment of diseases of the inflammatory and  
immune systems. Moreover, the expression of this gene product indicates a role in  
the regulation of the proliferation; survival; differentiation; and/or activation of  
hematopoietic cell lineages, including blood stem cells. This gene product may be  
30 involved in the regulation of cytokine production, antigen presentation, or other  
processes that may also suggest a usefulness in the treatment of cancer (e.g. by  
boosting immune responses). Since the gene is expressed in cells of lymphoid origin,



the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 412 of SEQ ID NO:95, b is an integer of 15 to 426, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 86

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: LERLGVGRGLE (SEQ ID NO:807),  
DLPPCWTTLKEHQCFMQYQLFTIQCKVVEQTICEDERKMESTCLTLXPESV

RQXCPATLWSSMNIC (SEQ ID NO:808), and/or

TNRVXLSWRKEEQRMGRTETGAKDKGRDFLERGSRGWQLYTGAADTEEV

(SEQ ID NO:809). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,

5 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the

10 invention.

This gene is expressed in activated neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

15 inflammation and immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the inflammatory and immune system, expression of this gene at significantly higher or lower levels may be routinely

20 detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 334 as residues: Met-1 to Gly-6, Gly-32 to Pro-43, Leu-55 to Gln-60.

The tissue distribution in neutrophils indicates that the protein products of this gene are useful for diagnosis and treatment of disorders of the immune and inflammatory system. Moreover, the expression of this gene product indicates a role

30 in the regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 830 of SEQ ID NO:96, b is an integer of 15 to 844, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

EQVLALLWPRFELILEMNVQSVRSTDPQRLGGLDTRPHYTTRRYAEFSSALVSI  
NQ TIPNERTMQLLGQLQVEVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVL  
MERAADDSKEVESFQQLNARTQEFIEELLSPPFGGLVAFVKEAEALIERGQA  
ERLRGEEARVTQLIRGFGSSWKSSVESLSQDVMRSFTNFRNGTSIIQG (SEQ ID  
5 NO:810), ALLKYRFFYQFLGNERATAKEIRDEYVETLSKIYLSYYRSYL  
GRLMKVQYEEVAEKDDLGMGVEDTAKKGFXSKPSLRSRNTIFTLGTGRGSVISP  
TELEAPILVPHTAQR (SEQ ID NO:811),  
EQRYPF EALFRSQHYXLLDNSCREYLFICEFFVVSGPXAHDLFHAVMGRTLS  
MTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPALDRYW (SEQ ID  
10 NO:812), GGLDTRPHYTTRRYAEFSSALVSINQ (SEQ ID NO:813),  
SRKEQLVFLINNYDMMLGVL (SEQ ID NO:814),  
ALLKYRFFYQFLGNERATAKEIRDEYVETLSKIYLSYYRSYLGRLMKVQYE  
EVAEKDDLGMGVEDTAKKGFXSKPSLRSRNTIFTLGTGRGSVISPTELEAPILVPH  
TAQRXEQRYPF EALFRSQHYXLLDNSCREYLFICEFFVVSGPXAHDLFHAVM  
15 GRTLSMTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPALDRYWEQ  
VLALLWPRFELILEMNVQSVRSTDPQRLGGLDTRPHYTTRRYAEFSSALVSIN  
QTIPNERTMQLLGQLQVEVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVL  
MERAADDSKEVESFQQLNARTQEFIEELLSPPFGGLVAFVKEAEALIERGQA  
ERLRGEEARVTQLIRGFGSSWKSSVESLSQDVMRSFTNFRNGTS (SEQ ID  
20 NO:815),  
PADLRAVSGTSEVGLM LLELHHKVVNVD ELSPGREGSELRLGQHPVEAMIEL  
DQLGQRSLNDTGAISEVGETPHYILTQRFH (SEQ ID NO:816), and/or  
GPHPGASHSAA XEQRYPF EALFRSQHYXLLDNSCREYLFICEFFVVSGPXAHD  
LFHAVMGRTLSMTLKHLD SYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPAL  
25 DRYWG TGACLAMATV (SEQ ID NO:817). Moreover, fragments and variants of  
these polypeptides (such as, for example, fragments as described herein, polypeptides  
at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these  
polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under  
stringent conditions, to the polynucleotide encoding these polypeptides ) are  
30 encompassed by the invention. Antibodies that bind polypeptides of the invention are  
also encompassed by the invention. Polynucleotides encoding these polypeptides are  
also encompassed by the invention.

The translation product of this gene shares sequence homology with a suppressor of actin mutation which is thought to be important in mutation suppression.

This gene is expressed primarily in fetal liver.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic or metabolic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver or cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another  
15 tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 335 as residues: Val-53 to Arg-60, Thr-88 to Thr-94, Ala-142 to Ser-150, Gly-  
20 188 to Glu-196, Gly-208 to Ser-214, Thr-227 to Gly-232, Lys-279 to Phe-285.

The tissue distribution in liver, combined with the homology to a highly conserved suppressor of actin mutation, suggest that the protein product of this gene is useful for diagnosis and treatment of liver disorders or cancer. Similarly, the protein product of this gene is useful for the detection and treatment of  
25 hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed  
30 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1971 of SEQ ID NO:97, b is an integer of 15 to 1985, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

#### *FEATURES OF PROTEIN ENCODED BY GENE NO: 88*

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

YEGKEFDYVFSIDVNEGGPSYKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQ  
 VAKFIIDNTKGQMLGLGNPSFSDPFTGGGRYVPGSSGSSNTLPTADPFTGAGR  
 YVPGSASMGTTMAGVDPFTGNSAYRSAASKTMNIYFPKKEAVTFDQANPTQI  
 LGKLKELNGTAPEEKKLTEDDLILLEKILSLICNSSSEKPTVQQLQILWKAINCP  
 EDIVFPALDILRLSIKHPNVNENFCNEKEGAQFSSHLINLLNPKGKPANQLLAL  
 RTFCNCFVGQAGQKLMMSQRESLMSHAIELKSGSNKNI (SEQ ID NO:818),  
 HIALATL ALNYSVCFHKD (SEQ ID NO:819),  
 HNIEGKAQCLSLISTILEVVQDLEATFRLLVALGTLISDDSNVQLAKS (SEQ  
 ID NO:820), LGVDSQIKKYSSVSEPAKVSECCRFILNLL (SEQ ID NO:821),  
 YEGKEFDYVFSIDVNEGGPSYKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQ  
 VAKFIIDNTKGQMLGLGNPSFSDPFTGGGRYVPGSSGSSNTLPTADPFTGAGR  
 YVPGSASMGTTMAGVDPFTGNSAYRSAASKTMNIYFPKKEAVTFDQANPTQI  
 LGKLKELNGTAPEEKKLTEDDLILLEKILSLICNSSSEKPTVQQLQILWKAINCP  
 EDIVFPALDILRLSIKHPNVNENFCNEKEGAQFSSHLINLLNPKGKPANQLLAL  
 RTFCNCFVGQAGQKLMMSQRESLMSHAIELKSGSNKNIHIALATLALNYSVC  
 FHKDHNIEGKAQCLSLISTILEVVQDLEATFRLLVALGTLISDDSNVQLAKSL

GVDSQIKKYSSVSEPAKVSECCRFILNLL (SEQ ID NO:822),  
 LNLLLITQKVKCWDLGIPAFQIHLQVVVG (SEQ ID NO:823),  
 IKHPSVNENFCNEKEGAQFSSHLINLLNP (SEQ ID NO:824),  
 AIELKSGSNKNIHIALATLALN (SEQ ID NO:825),  
 5 VQLAKSLGVDSQIKKYSSVSEPA (SEQ ID NO:826),  
 YEGKEFDYVFSIDVNEGGPSYKLPYN (SEQ ID NO:827),  
 AYNFLQKNDLNPFLDQVAK FIIDNT (SEQ ID NO:828),  
 SFSDPFTGGGRYVPG (SEQ ID NO:829), TADPFTGAGRY (SEQ ID NO:830),  
 TTMAGVDPFTGNSAYRSAA (SEQ ID NO:831), NIYFPKKEA (SEQ ID NO:832),  
 10 TFDQANPTQILGKLKELNG (SEQ ID NO:833),  
 PEDIVFPALDILRLSIKHPSVNENFCNEKE (SEQ ID NO:834),  
 QFSSHLINLLNPKG KPANQLLALRTFCNCFV (SEQ ID NO:835), and/or  
 QAGQKLMMSQRESLMSHAIELKSGSN (SEQ ID NO:836). Moreover, fragments  
 and variants of these polypeptides (such as, for example, fragments as described  
 15 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
 identical to these polypeptides and polypeptides encoded by the polynucleotide which  
 hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 20 these polypeptides are also encompassed by the invention.

These polypeptides share significant homology with phospholipase A2  
 activating protein, which is thought to be important in signal transduction (see, e.g.,  
 Wang et al., Gene 161(2):237-241 (1995)). The gene encoding the disclosed cDNA is  
 believed to reside on chromosome 9. Accordingly, polynucleotides related to this  
 25 invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in endothelial cells, to a less extent in  
 placenta, endometrial stromal cells, osteosarcoma, testis tumor, muscle, and infant  
 brain that are likely to be rich in blood vessels.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 disorders of the vascular system, aberrant angiogenesis, tumor angiogenesis, or

related disorders of endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system or tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial, placenta, skeletal, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in endothelial cells and several potential highly vascularized tissues, combined with the homology to the highly conserved phospholipase A2 activating protein suggest that this gene may be involved in transducing signals for endothelial cells in angiogenesis or vasculogenesis. Furthermore, the protein may show utility for the treatment, and/or prevention of embolism, thrombosis, aneurysm, atherosclerosis, microvascular disease, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1402 of SEQ ID NO:98, b is an integer of 15 to 1416, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 89**



In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRT  
5 ISAYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPP  
CLLSTVQYISSFYASCLSGEESYWWMQFTA AVE (SEQ ID NO:837),  
YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRT  
ISAYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPP  
CLLSTVQYISSFYASCLSGEESYWWMQFTA AVEFIKTI (SEQ ID NO:838),  
10 YPNQDGDILRDQVL (SEQ ID NO:839), EAPWPSAQSEI (SEQ ID NO:840),  
PVLVFLIKANP (SEQ ID NO:845), SGEESYWWMQFTA AVEFIKTI (SEQ ID  
NO:841), ADDFVPVLVFLIK ANPP (SEQ ID NO:842), YKTPRDKVQCIL (SEQ  
ID NO:843), and/or GADDFVPV LVFLIK (SEQ ID NO:844). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
15 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
20 these polypeptides are also encompassed by the invention.

The translation product of this gene shares sequence homology with human Ras inhibitor and yeast VPS9p which is thought to be important in Golgi vacuole transport. The gene encoding the disclosed cDNA is believed to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a  
25 marker in linkage analysis for chromosome 9.

This gene is expressed primarily in T cells and melanocytes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
30 immune, hematopoietic, or integumentary disorders, such as dysfunctions and disorders involving T cells and melanocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and melanocytes, combined with the homology to a Ras inhibitor, indicates that the protein product of this gene is useful for regulating signal transduction; the diagnosis and treatment of disorders involving T cells and melanocytes, and potentially in the prevention or study of immune responses to aberrant integumentary cells and tissues, particularly in tumors and cancers, such as skin cancers. Moreover, the protein product of this gene is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1746 of SEQ ID NO:99, b is an integer of 15 to 1760, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 90**

The translation product of this gene shares sequence homology with neuronal olfactomedin-related ER localized protein which is thought to be important in the maintenance, growth, or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. Moreover, the protein also shares homology with the conserved human AMY protein which is thought to be a glial cell-specific transforming protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

25 SARASTQPPAGQHGPC (SEQ ID NO:846),  
MPGRWRWQRDMHPARKLLSLLFLILMGTELTQD (SEQ ID NO:847),  
SAAPDSLLRSSKGSTRGSL (SEQ ID NO:848), AAIVTWRGKSESRIAKTPGI  
(SEQ ID NO:849), FRGGGTLVLPHTTPEWLIL (SEQ ID NO:852),  
PLGITLPLGAPETGGGD (SEQ ID NO:850), NSARAS  
30 TQPPAGQHGPCMPGRWRWQRD (SEQ ID NO:853),  
YIVQGTTSPFEMPTIPTPARHRAPHSPAGHVATAPQALHIKPAMHTAGRHAG  
CPSRSQ RHNPHRLFLEPPRAALCPKGG (SEQ ID NO:854),

ASNAHSWPARWLFPQVSAAQSPPPVSGAPKGSVMPKGRMSHSGVCVGGRTK  
VPPPLKMPGVLAIRLSLFPLQMTIAAKDPLVLPFELLSRESGAAES (SEQ ID  
NO:855), GRMSHSGVCVGGRTKVPPPLKMPGVLA (SEQ ID NO:856), and/or  
CAAETWKGSQRAGQLCALLA (SEQ ID NO:851). Moreover, fragments and  
5 variants of these polypeptides (such as, for example, fragments as described herein,  
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
under stringent conditions, to the polynucleotide encoding these polypeptides ) are  
encompassed by the invention. Antibodies that bind polypeptides of the invention are  
10 also encompassed by the invention. Polynucleotides encoding these polypeptides are  
also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
9. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 9.

15 This gene is expressed in pineal gland.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
neurological and endocrine disorders. Similarly, polypeptides and antibodies directed  
20 to these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the neurological or endocrine systems, expression of  
this gene at significantly higher or lower levels may be routinely detected in certain  
tissues or cell types (e.g., neural, endocrine, and cancerous and wounded tissues) or  
25 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
another tissue or cell sample taken from an individual having such a disorder, relative  
to the standard gene expression level, i.e., the expression level in healthy tissue or  
bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
30 NO: 338 as residues: Leu-20 to Ala-26, Arg-32 to Arg-39, Thr-104 to Gly-112.

The tissue distribution in pineal gland, combined with the homology to both  
the olfactomedin-related, and AMY proteins, indicates that the protein product of this

gene is useful for maintenance, growth, or differentiation of neuron cells in pineal gland. Therefore, the protein product of this gene may be useful for the diagnosis and treatment of neurological disorders in pineal gland. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 585 of SEQ ID NO:100, b is an integer of 15 to 599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 91

This gene is expressed primarily in prostate and apoptotic T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, or hematopoietic disorders, particularly prostate disease and T cell dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate and T-cells indicates that the protein product of this gene is useful for the detection of abnormal activity in prostate and T cells, such as proliferative conditions of the prostate, or possibly treatment of this abnormality. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial

utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 770 of SEQ ID NO:101, b is an integer of 15 to 784, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 92**

The gene encoding the disclosed cDNA is believed to reside on chromosome  
20 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in prostate, and to a lesser extent, in smooth muscle cells, fibroblasts, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in prostate or vascular tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
30 the above tissues or cells, particularly of the prostate or vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, musculoskeletal, cancerous and wounded tissues)

or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5        Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 340 as residues: Ser-38 to Lys-46.

      The tissue distribution in prostate and smooth muscle indicates that the protein product of this gene is useful for regulating the function of prostate or highly vascularized tissues, such as the placenta. Similarly, the protein product of this gene  
10       may be useful in the treatment and/or detection of vascular disorders which include, but are not limited to, stroke, embolism, thrombosis, aneurysm, microvascular disease, or atherosclerosis. The protein may also show utility in the treatment or detection of proliferative disorders of the prostate or male reproductive system.

      Protein, as well as, antibodies directed against the protein may show utility as a tumor  
15       marker and/or immunotherapy targets for the above listed tissues.

      Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
20       excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 390 of SEQ ID NO:102, b is an integer of 15 to 404, where both a and b correspond to the positions of nucleotide  
25       residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 93

30       In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GHQTAPETPSRSD (SEQ ID NO:857). Moreover, fragments and variants of this polypeptide (such as, for



example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind  
5 polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in embryos and fetal tissues, and to a lesser extent, in proliferative tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in embryonic development and cell proliferation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
15 disorders of the above tissues or cells, particularly of the embryonic tissues and proliferative cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, differentiating, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue  
20 or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in embryonic and fetal tissues indicates that the protein product of this gene is useful for the diagnosis or treatment of abnormalities in  
25 developing and proliferative cells and organs. Similarly, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation  
30 and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2204 of SEQ ID NO:103, b is an integer of 15 to 2218, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 94

The translation product of this gene shares sequence homology with a transformation related protein which is thought to be important in transformation.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: SQTDR (SEQ ID NO:858). Polynucleotides encoding this polypeptides are also encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in female reproductive tissues, i.e., breast cancer cells, placenta, and ovary, and to a lesser extent, in fetal lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer or dysfunction of reproductive tissues, in addition to pulmonary or

developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproduction system, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, reproductive, ovarian, breast, placental, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

10 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 342 as residues: Ser-50 to Pro-61.

The tissue distribution in female reproductive tissues, combined with the

15 homology to the transformation related protein, indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions caused by transformation, i.e. tumorigenesis in reproductive organs, (e.g. breast, placenta, and ovary). Similarly, expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of

20 cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein may also be useful in the treatment or detection of a

25 variety of pulmonary conditions, including, but not limited to emphysema, ARDS, cystic fibrosis, asthma, etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1337 of SEQ ID NO:104, b is an integer of 15 to 1351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 95

10

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

NIYFKEKRKRGGAKMAGAIEN (SEQ ID NO:859),

VYLCAYTSTINVTVTANAKLINMCCLVDSNTRSCVVIDEGIFRSAEQFLIKFR

15 NKQSTIFPRFTWELHSIGLVFSIVFMGWCIQEHQSKDIQPHPIDACEKGTVHL  
DCDAAPFPMAFRYLTNDEEDDSHGSAGQGDKHEELEPKN (SEQ ID NO:860),  
KMPCRMSPNSSIQVQSNPMENHSTGILIKVMEIPRAKMTFSRSTGGRDIMVILL  
QYHTIMMKMLGVRKVFMANHTLVKPPFWWIPTNRISFISPIPTLIFFFSFTGSR  
MFKR (SEQ ID NO:861),

20 TTKSEKMQKSPWTFPWLTVMTHLLSGLKWPMKEYHGNSNAPSHLPRLQSM  
RAVTMNVMSFLSWKLGLWPISFTF (SEQ ID NO:862),

IKFRNKQSTIFPRFTWELHSIGLVFSIVFMG (SEQ ID NO:863),

SSIQVQSNPMENHSTGILIKVMEIPRAKM (SEQ ID NO:864), and/or

LGVRKVFMANHTLVKPPFWWIPTNRISFISPIP (SEQ ID NO:865). Moreover,

25 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
30 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

5           This gene is expressed primarily in testes, rhabdomyosarcoma, infant brain and to a lesser extent in some tumors and highly vascularized tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, 10 tumorigenesis, abnormal angiogenesis, reproductive, vascular, and/or neurological disorders. , Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor tissues or vascular tissues, expression of this gene at 15 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, neural, developmental, vascular, reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene 20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 343 as residues: Arg-46 to Trp-54, Pro-60 to Ile-69, Asn-116 to Ala-122, Arg- 147 to Lys-153, Ser-158 to Glu-170, Ile-399 to Ser-405, Pro-486 to Met-499, Pro-502 25 to Asp-508.

The tissue distribution in infant brain indicates that the protein product of this gene is useful for a range of disease states including treatment of tumor or vascular disorders and the treatment of neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, 30 obsessive compulsive disorder and panic disorder. Moreover, expression within vascular tissues indicates that the protein product of this gene is useful in the treatment and/or detection of a variety of vascular conditions, which include but are

not limited to emphysema, atherosclerosis, thrombosis, microvascular disease, stroke or aneurysm. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2052 of SEQ ID NO:105, b is an integer of 15 to 2066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 96

The translation product of this gene is homologous to the *Clostridium*  
perfringens enterotoxin (CPE) receptor gene product and shares sequence homology  
20 with a human ORF specific to prostate and a glycoprotein specific to oligodendrocytes, both of which are tissue specific proteins. See e.g., Katahira et al. J Cell Biol. 136(6):1239-1247 (1997). PMID: 9087440; UI: 97242441.

In specific embodiments, polypeptides of the invention comprise, or  
alternatively consist of, the following amino acid sequences: TMA SMGLQV (SEQ  
25 ID NO:866),

KSWMMLWAVQDTGTITIRPANRNTTPATIMVLALALSSSRQLVHLPPTTDSST  
PRAATMMLMMTRARAACRSCGSASSES YTLHCTIWPVLCTTQFIHRPSQMVCE  
VTMLLPMKAVTRHMGSAQHSM T ASQPRTASAMPITCSPMEAI VQRPRELRT  
WKAEGIRLWGP (SEQ ID NO:867),  
30 LQVMGIALAVLGWLAVMLCCALPMWRVT (SEQ ID NO:868),  
SNIVTSQTIWEG LWMNCVVQST (SEQ ID NO:869),  
QMCKVYDSL LALPQDLQ (SEQ ID NO:870),

KCTNCLEDESAKAKTMIV(SEQ ID NO:871),  
GVVFLLAGLMVIVPVSWTAHNIIQDFYNPLVA (SEQ ID NO:872), and/or  
CCNCPRTDKPY (SEQ ID NO:873). Moreover, fragments and variants of these  
polypeptides (such as, for example, fragments as described herein, polypeptides at  
5 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
conditions, to the polynucleotide encoding these polypeptides ) are encompassed by  
the invention. Antibodies that bind polypeptides of the invention are also  
encompassed by the invention. Polynucleotides encoding these polypeptides are also  
10 encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
7. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 7.

This gene is expressed primarily in pancreas tumor and ulcerative colitis, and  
15 to a lesser extent in several tumors and normal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
metabolic, gastrointestinal, or proliferative disorders, such as pancreatic disorders,  
20 ulcerative colitis, tumors and food poisoning. Similarly, polypeptides and antibodies  
directed to these polypeptides are useful in providing immunological probes for  
differential identification of the tissue(s) or cell type(s). For a number of disorders of  
the above tissues or cells, particularly of the digestive system or tumorigenic system,  
expression of this gene at significantly higher or lower levels may be routinely  
25 detected in certain tissues or cell types (e.g., metabolic, gastrointestinal, pancreatic,  
and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum,  
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
from an individual having such a disorder, relative to the standard gene expression  
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
30 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 344 as residues: Gly-147 to Met-152, Cys-177 to Lys-188.

The tissue distribution in pancreas, combined with the homology to a prostate and oligodendrocyte-specific protein, indicates that the protein product of this gene is useful as a marker for the diagnosis or treatment of disorders in pancreas, ulcerative colitis, and tumors. Furthermore, identity to the human receptor for *Clostridium* 5 *perfringens* enterotoxin indicates that the soluble portion of this receptor could be used in the treatment of food poisoning associated with *Clostridia perfringens* by blocking the activity of the *perfringens* enterotoxin. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

10 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is 15 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1691 of SEQ ID NO:106, b is an integer of 15 to 1705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

20

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 97

25 The translation product of this gene shares sequence homology with an ATPase from *Saccharomyces cerevisiae* which is thought to be important in metabolism (See Genbank Accession No.g1181253).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: PFTALAGSEIFSLIE 30 (SEQ ID NO:874), SKTEALTQAFR (SEQ ID NO:875), VVHTVSLHEIDVINSRTQGFLALF (SEQ ID NO:876), PGVLFIDEVHMLDIE (SEQ ID NO:877),



- AGIRQRF SARLWQLVSIMATVTATTKVPEIRDVTRIERIGAHSHIRGLGLDDAL  
EPRQASQGMV GQLAARRAAGVVLEMIREGKLAGRAVLIAGQP GTGKTAIAM  
GMAQALGPDTPFTAIAGSEIFSLEMSKTEALTQAFRRSIGVRIKEETEIEGEVV  
EIQIDRPATGTGSKVGKLT LKTTEMETTYDLG TKMIXSLTKDKVQAGDVTID  
5 KATGKISKLG RSFTRARELRRYGLPDQVRAVPRWGAPETQGGGAHRVPARD  
RRHQLSHPLPGALLR (SEQ ID NO:878),  
SPSTRRRARSPSWAAPSHAPANYDAMGSQTKFVQCPDGELQKRKEVVHTVS  
LHEIDVINSRTQGFLALFSGDTGEIKSEVREQINAKVAEWREEGKAEIIPGVLF  
DEVHMLDIESFSFLNRALES DMAPVQQVYGDAVRALVAGAPDSRDATVGGL  
10 VPNSCSPGDPLVLERPPPRWXS (SEQ ID NO:879),  
WIPRAAGIRHEATNRGITRIRGTSYQSPHGIPIDLLDRRHVTLQGPVEEGEALD  
VQHVDLVDEQHSRDD LRLALLAPLSHLGIDLLTDF (SEQ ID NO:880),  
YDAMGSQTKFVQCPDGELQKRKEVVHTVSL (SEQ ID NO:881),  
KAEIIPGVLFIDEVHMLDIESFSFLNRALES (SEQ ID NO:882), and/or  
15 EATNRGITRIRGTSYQSPHGIPIDLLDR (SEQ ID NO:883). Moreover, fragments  
and variants of these polypeptides (such as, for example, fragments as described  
herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
identical to these polypeptides and polypeptides encoded by the polynucleotide which  
hybridizes, under stringent conditions, to the polynucleotide encoding these  
20 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes and several hematopoietic cells.

- Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
reproductive, immune, or hematopoietic disorders, particularly male infertility and  
leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are  
useful in providing immunological probes for differential identification of the  
30 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
particularly of the hematopoietic system, expression of this gene at significantly  
higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,

reproductive, immune, hematopoietic, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
5 healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes and hematopoietic cells, combined with the homology to ATPases, indicates that the protein product of this gene is useful as a marker for the diagnosis and treatment of leukemia and other hematopoietic disorders. The protein may also show utility as a contraceptive, or for the treatment and/or  
10 detection of aberrant testicular function. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or  
15 induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds); stimulation of follicle stimulating hormone (for  
20 control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of  
25 the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1153 of SEQ ID NO:107, b is an integer of 15 to 1167, where both a and b correspond to the positions of nucleotide  
 5 residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 98

10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 MRSARPSLGCLPSWAFSQUALNI (SEQ ID NO:884),  
 LLGLKGLAPAEISAVCEGNFN (SEQ ID NO:885),  
 VAHGLAWSYYIGYLRLILPELQARIR (SEQ ID  
 15 NO:886), TYNQHYNNLLRGAVSQRC (SEQ ID NO:887), ILLPLDCGVDPNLS  
 MADPNIRFLDKLPQQTGDRAGIKDRVYSN (SEQ ID NO:888),  
 SIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSGEDRLEQ (SEQ ID  
 NO:889),  
 AKLFCRTLEDILADAPESQNNCRLLIAYQEPADDSSFSLSQEVLRLRLRQEEKEE  
 20 VTVGSLKTSAPSTSTMSQEPPELLISGMEKPLPLRTDFS (SEQ ID NO:890),  
 LRLHSEKLPLAARSAGPSLLVIIQSSQCPGRRYRGSYWRTVRACLGCPLRRG  
 ALLLLSIYFYYSPLNAVGPFTW (SEQ ID NO:892),  
 VWLTPTFASWINCPSRPVTVLASRIGFTATASMSFWRTGSGRAPVSWSTPPPC  
 RLCLPCHNTVKLALAGRIGLSRPNSSAGHLRTSWQMPLSLRTTAASLPTRNLQ  
 25 MTAASRCPRRFSGTCGRRKRKRLWAA (SEQ ID NO:893),  
 GVCQVSFMGPSRPTPHPSPLPLPGDAELSQWYQQAPSPSGSWSCSIIGEPQQK  
 NGEIEEEAEFGVLNPPAPTLQHQCGLSCRATLA (SEQ ID NO:894), and/or  
 LLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPEL (SEQ ID  
 NO:891). Moreover, fragments and variants of these polypeptides (such as, for  
 30 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by  
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in prostate BPH, and to a lesser extent, in bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, hematopoietic, or immune disorders, particularly benign prostatic hypertrophy, prostate cancer, or leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male urinary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, hematopoietic, immune, prostatic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 346 as residues: Ile-60 to Asn-69, Leu-106 to Asp-112, Glu-130 to Gly-136, Phe-160 to Glu-167, Pro-184 to Cys-190, Glu-197 to Ser-202, Arg-215 to Glu-221, Thr-237 to Pro-242.

25 The tissue distribution in prostate tissue indicates that the protein product of this gene is useful for the diagnosis or treatment of reproductive disorders, such as benign prostatic hypertrophy or prostate cancer. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may

also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:108, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 99

The gene encoding the disclosed cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

25 This gene is expressed primarily in salivary gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, particularly of the salivary gland. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of glandular tissues, expression of

this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. salivary gland, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, chyme, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative  
5 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in salivary glands indicates that the protein product of this gene is useful for the treatment and/or detection of disorders of or injuries to the salivary gland or other glandular tissue. Protein, as well as, antibodies directed  
10 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:109 and may have been publicly available prior to conception  
15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 597 of SEQ ID NO:109, b is an  
20 integer of 15 to 611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 100**

25

The translation product of this gene shares sequence homology with a *C.elegans* gene. Based upon its degree of conservation, an important cellular function can be attributed to this protein. When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating  
30 sequence) promoter element. Thus, it is likely that this gene activates T-cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-

STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 DPRVRLNSLTCKHIFISLTQ (SEQ ID NO:902),  
 TMKLLKLRNIVKLSLYRHFTN (SEQ ID NO:895),  
 TLILAVAASIVFIIWTTMKFRI (SEQ ID NO:896),  
 10 VTCQSDWRELWVDDAIWRLLFSMILFVI (SEQ ID NO:897),  
 MVLWRPSANNQRFAFSPLSEEEEEDEQ (SEQ ID NO:898),  
 MVLWRPSANNQRFAFSPLSEEEEEDEQ (SEQ ID NO:899),  
 KEPMLKESFEGMKMRSTKQEPNGNSKVNKAQEDDL (SEQ ID NO:900),  
 NAFGRHSTAVK (SEQ ID NO:903),  
 15 ESCLLCGISEYPIQRXICPGCFDPCRXAFSSETLTGSNPGHHSQSGIWHRQATP  
 GVTLHKVVVAXALYLLFSGMEGVLRVTGAQTDLASLAFIPLAFLDTALCWW  
 IFISLTQTMKLLKLRNIVKLSLYRHFTNTLILAVAASIVFIIWTTMKFRIVTCQ  
 SDWRELWVDDAIWRLLFSMILFVIMVLWRPSANNQRFAFSPLSEEEEEDEQK  
 EPMLKESFEGMKMRSTKQEPNGNSKVNKAQEDDLKWVEENVPSVTDVALP  
 20 ALLDSDEERMITHFERSKME (SEQ ID NO:904), and/or  
 KWVEENVPSVTDVALPALLDSDEERMITHFERSKME (SEQ ID NO:901).  
 Moreover, fragments and variants of these polypeptides (such as, for example,  
 fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
 25 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.  
 Polynucleotides encoding these polypeptides are also encompassed by the invention.  
 The gene encoding the disclosed cDNA is believed to reside on chromosome  
 30 15. Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 15.

This gene is expressed primarily in thyroid, and to a lesser extent, in osteoclastoma, kidney medulla, and lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine disorders, particularly thyroid dysfunction or cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, skeletal, urogenital, renal, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 348 as residues: Lys-107 to Leu-124, Glu-150 to Thr-159, Pro-173 to Asp-179, Ser-192 to Ser-201.

The tissue distribution in thyroid, combined with the detected GAS biological activity, indicates that the protein product of this gene is useful for the diagnosis and treatment of thyroid dysfunction or cancer. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:110 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2618 of SEQ ID NO:110, b is an



integer of 15 to 2632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 101

The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: YEPMDFXMALIYD (SEQ ID NO:905), IRHELTVLRDT RPACA (SEQ ID NO:906), and/or MDFXMALYD (SEQ ID NO:907). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, 15 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are 20 also encompassed by the invention.

This gene is expressed primarily in kidney cortex, and to a lesser extent, in adult brain, corpus colosum, hippocampus, and frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample 25 and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, kidney disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and renal system, 30 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult brain, corpus colosum, hippocampus, and  
5 frontal cortex indicates that the protein product of this gene is useful for treatment or diagnosis of neurological disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep  
10 patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, The tissue distribution in kidney indicates that this gene or gene product could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal  
15 tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
20 and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:111 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2235 of SEQ ID NO:111, b is an integer of 15 to 2249, where both a and b correspond to the positions of nucleotide  
30 residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 102**

The translation product of this gene shares sequence homology with F15C11.2 of *C. elegans* which is of unknown function.

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 MQEMMRNQDRALSNLESIPGGYNA (SEQ ID NO:908),  
 LRRMYTDIQEPMLSAAQEFGGNPF (SEQ ID NO:909),  
 ASLVSNTSSGEGSQPSRTENRDPLPNWAPQT (SEQ ID NO:910),  
 10 SQSSSASSGTASTVGGTTGSTASGTSGQSTTAPNLVPGVGASMFNTPGMQSL  
 QQITENPQLMQNMLSAPY (SEQ ID NO:911),  
 MRSMMQSLSQNPDLAAQMMLNPLFAGNPQLQEQMRQQLPTFLQQ (SEQ  
 ID NO:912),  
 MQNPDTLSAMSNPRAMQALLQIQQLQTLATEAPGLIPGFTPGLGALGSTGG  
 15 SSGTNGSNATPSENTSPTAGT (SEQ ID NO:913),  
 TEPGHQQFIQQLQALAGVNPQLQNPEVRFQQQLQQLSAMGFLNREANLQA  
 LIATGGDINAAIERLLGSQPS (SEQ ID NO:914),  
 RNPAMMQEMMRNQDRALSNLESIPGGYNALRRMYTDIQEPMLSAA (SEQ ID  
 NO:915), GNPFASLVSNTSS (SEQ ID NO:916), ENRDPLPNPWA (SEQ ID  
 20 NO:917), GKILKDQDTLSQHGHD (SEQ ID NO:918), GLTVHLVIKTQNR  
 P (SEQ ID NO:919), SELQSQMQRQLLSNPPEMM (SEQ ID NO:920),  
 PEISHMLNPNPDIMR (SEQ ID NO:921), and/or RQLIMANPQMQLIQRNP (SEQ  
 ID NO:922). Moreover, fragments and variants of these polypeptides (such as, for  
 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
 25 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by  
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides ) are encompassed by the invention. Antibodies that  
 bind polypeptides of the invention are also encompassed by the invention.  
 Polynucleotides encoding these polypeptides are also encompassed by the invention.
- 30 This gene is expressed primarily in breast.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of tumor systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. breast, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast indicates that the protein product of this gene is useful for treatment and diagnosis of some types of breast cancer. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:112 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2184 of SEQ ID NO:112, b is an integer of 15 to 2198, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 103**

The translation product of this gene shares sequence homology with secreted serine proteases and lysozyme C precursor, which is thought to be important in bacteriolytic function.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

NLCHVDCQDLLNPNNLAGIHCAKRIVS (SEQ ID NO:923),

LDGFEGYSLSDWLCLAFVESKFN (SEQ ID NO:924),

5 NENADGSFDYGLFQINSHYWCN (SEQ ID NO:925),

NLCHVDCQDLLNPNNLAGIHCAKRIVS (SEQ ID NO:926), and/or

EPSALSCTSSPPR (SEQ ID NO:927). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides

10 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infection, immune system disorders, reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. testes, cancerous and

20 wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 351 as residues: Ile-62 to Phe-70, Asn-78 to Asn-84.

The tissue distribution in testes, combined with the homology to lysozyme C precursor indicates that the protein product of this gene is useful for boosting the monocyte-macrophage system, and for enhancing the activity of immune agents. Alternatively, the tissue distribution indicates that the protein product of this gene is  
5 useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is  
10 believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone  
15 formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:113 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1029 of SEQ ID NO:113, b is an integer of 15 to 1043, where both a and b correspond to the positions of nucleotide  
25 residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 104**

30 This gene is expressed primarily in apoptotic T-cell, and to a lesser extent in CD34(+) cells..

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these

5 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,

10 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene

15 is useful for treatment and diagnosis of some immune disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the

20 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion

25 of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed

30 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:114 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
 5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 689 of SEQ ID NO:114, b is an integer of 15 to 703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 105**

The translation product of this gene shares sequence homology with ARI protein of Drosophila (See Genbank Accession 2058299; EMBL: locus  
 15 DMARIADNE, accession X98309), which is thought to be important in axonal path-finding in the central nervous system.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 IREVNEVIQNPAT (SEQ ID NO:928),  
 20 ITRILLSHFNWDKEKLMERYFDGNLEKLFA (SEQ ID NO:929),  
 NTRSSAQDMPCQICYNYPNSYF (SEQ ID NO:930), TGL  
 ECGHKFCMQCWSEYLTTKIMEEGMGQTISCPAHG (SEQ ID NO:936),  
 CDILVDDNTVMRLITDSKVKLKYQHLITNSFVECNRLWKWCPAPDCHHVVKV  
 QYPPDAKPV (SEQ ID NO:931),  
 25 CDILVDDNTVMRLITDSKVKLKYQHLITNSFVECNRLWKWCPAPDCHHVVKV  
 (SEQ ID NO:932),  
 GCNHMVCRNQNCKAEFCWVCLGPWEPHGSAWYNCNRYNEDDAKAARDA  
 QERSRAALQRYL (SEQ ID NO:933),  
 FYCNRYMNMHMQSLRFEHKLYAQVKQKMEEMQQHNMSWIEVQFLKKAVDV  
 30 LCQCRATLMT (SEQ ID NO:934), and/or  
 YVFAFYLLKNNQSIIFENNQADLENATEVLSGYLERDISQDSLQDIKQKVQDK  
 YRYCESR (SEQ ID NO:935). Moreover, fragments and variants of these



polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in adult brain, and to a lesser extent in testes, endometrial tumor, melanocytes, and infant brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases or injuries involving axonal path development. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, testes, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult brain, combined with the homology to ARI protein indicates that the protein product of this gene is useful for the treatment of disease states or injuries involving axonal path development, including neurodegenerative diseases and nerve injury, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well

as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:115 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3670 of SEQ ID NO:115, b is an integer of 15 to 3684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 106**

The translation product of this gene shares sequence homology with cytochrome b561 [Sus scrofa] which is thought to be an integral membrane protein of neuroendocrine storage vesicles of neurotransmitters and peptide hormones. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in frontal cortex, and to a lesser extent in rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 354 as residues: Ser-18 to Pro-24.

The tissue distribution in frontal cortex, combined with the homology to cytochrome b561 [*Sus scrofa*] indicates that the protein product of this gene is useful for the treatment and diagnosis of neurological disorders. This gene may also be important in the regulation of some types of cancers. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the brain and nervous system. Elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:116 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1951 of SEQ ID NO:116, b is an integer of 15 to 1965, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 107**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MWGYLFVDAAWNFLGCLICGW (SEQ ID NO:937),

MHFISSGNVSAIRSSILLRLXSLSYLGNCRLVSAIFVYFLLFLLLS (SEQ ID

5 NO:938), and/or

MDQALRGSPSEGFTDPSPQVGRQIPSPWRRLVLPKASGCFLEREWWLCV

FKLRTRPGAEAHAYNSSILGGRGKGIT (SEQ ID NO:939). Moreover, fragments

and variants of these polypeptides (such as, for example, fragments as described

herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%

10 identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in pancreas tumor, and to a lesser extent in cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

20 pancreatic tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

25 types (e.g. pancreas, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 355 as residues: Pro-22 to Phe-33.

The tissue distribution in pancreas tumors indicates that the protein product of this gene is useful for diagnosis and treatment of pancreatic tumors, and/or tumors of metabolic tissues and cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the  
 5 above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:117 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
 10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 489 of SEQ ID NO:117, b is an integer of 15 to 503, where both a and b correspond to the positions of nucleotide  
 15 residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 108

20 The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

25 MLPALASCCHFSPPEQAARLKKLQEQEKQQKVEFRKRMEKEVSDFIQDSGQI  
 KKKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYVMIFKKEFAPSDEELD  
 SYRRGEEWDPQKAEEKRNXKELAQRQ (SEQ ID NO:940),  
 EEEAAQQGPVVVSPASDYKDKYSHLIGKGAAKDAAHMLQANKTYGCXPVA  
 NKRDRSIEEAMNEIRAKKRLRQSGE (SEQ ID NO:941),  
 30 PPRRPAQLPLTPGAGQGAGRDKAAAIRAHPGAPPLNHLLP (SEQ ID NO:942),  
 AVPQAGGKQVFDLSPLELGYVRGMCVCV (SEQ ID NO:943) and/or  
 MLPALASCCHFSPPEQAARLKKLQEQEKQQKVEFRKRMEKEVSDFIQDSGQI

KKKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYVMIFKKEFAPSDEELD  
SYRRGEEWDPQKAEEKRNXKELAQRQEEEAQQGPVVVSPASDYKDKYSHL  
IGKGAAKDAAHMLQANKTYGCXPVANKRDTRSIEEAMNEIRAKKRLRQSGE

(SEQ ID NO:944). Moreover, fragments and variants of these polypeptides (such as,  
5 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides ) are encompassed by the invention.  
Antibodies that bind polypeptides of the invention are also encompassed by the  
10 invention. Polynucleotides encoding these polypeptides are also encompassed by the  
invention.

The translation product of this gene shares sequence homology with FSA-1,  
which may play a role as a structural protein component of the acrosome. The  
mammalian spermatozoon undergoes continuous modifications during  
15 spermatogenesis, maturation in the epididymis, and capacitation in the female  
reproductive tract. Only the capacitated spermatozoa are capable of binding the zona-  
intact egg and undergoing the acrosome reaction. The fertilization process is a net  
result of multiple molecular events which enable ejaculated spermatozoa to recognize  
and bind to the egg's extracellular coat, the zona pellucida (ZP). Sperm-egg  
20 interaction is a species-specific event which is initiated by the recognition and binding  
of complementary molecule(s) present on sperm plasma membrane (receptor) and the  
surface of the ZP (ligand). This is a carbohydrate-mediated event which initiates a  
signal transduction cascade resulting in the exocytosis of acrosomal contents. This  
step is believed to be a prerequisite which enables the acrosome reacted spermatozoa  
25 to penetrate the ZP and fertilize the egg. Recently, another group published this gene,  
calling it sperm acrosomal protein [Homo sapiens] (Proc. Natl. Acad. Sci. U.S.A.  
95 (14), 8175-8180 (1998)).

This gene is expressed primarily in fetal kidney and sperm.

Polynucleotides and polypeptides of the invention are useful as reagents for  
30 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
male reproductive disorders, especially involving acrosomal dysfunction. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. sperm, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10        Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 356 as residues: Met-12 to Gln-30, Lys-35 to Val-46, Arg-49 to Val-56, Gln-61 to Glu-77, Gly-96 to Cys-101, Glu-110 to Lys-139, Leu-141 to Gln-151, Ser-161 to Tyr-167, Asn-196 to Ile-203, Arg-211 to Ser-227.

15        The tissue distribution in sperm, combined with the homology to FSA-1 and the Homo sapiens sperm acrosomal protein indicates that the protein product of this gene is useful for the treatment of infertility due to acrosomal dysfunction of sperm. Protein may also be useful as a contraceptive either alone, or in combination with other therapies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20        Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:118 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
25        more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1057 of SEQ ID NO:118, b is an integer of 15 to 1071, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 109

This gene is expressed primarily in pituitary tissue, and to a lesser extent in epididymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. epididymus, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 357 as residues: Met-1 to Trp-6.

Because the gene is found in both pituitary and epididymus, this indicates that the protein product of this gene is useful for the treatment and diagnosis of male reproductive disorders. This may involve a secreted peptide produced in the pituitary targeting the epididymus. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:119 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:119, b is an



integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 110

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: LLCPVLNSGXSWNFFPHPSQPEYSFHGFHSTRLWI (SEQ ID NO:945), and/or  
10 PSTPWFLFLLGLTCPFSTSHPRWDSIPP (SEQ ID NO:946). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these  
15 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in resting T-cells. .

Polynucleotides and polypeptides of the invention are useful as reagents for  
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
25 particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of certain immune disorders, especially those involving T-cells. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:120 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 268 of SEQ ID NO:120, b is an integer of 15 to 282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 111**

The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

This gene is expressed primarily in cerebellum and whole brain, and to a lesser extent in infant brain and fetal kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 359 as residues: Asp-48 to Gly-55.

The tissue distribution in cerebellum and whole brain indicates that the protein product of this gene is useful for diagnosis and treatment of neurological disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:121 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2621 of SEQ ID NO:121, b is an integer of 15 to 2635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.

10

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 112

The translation product of this gene shares sequence homology with yeast mitochondrial ribosomal protein, which is homologous to ribosomal protein s15 of  
15 *E.coli*, which is thought to be important in the early assembly of ribosomes (See Genbank Accession No. M38016). The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in developmental tissues.

20

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development of cancers and tumors in addition to healing wounds. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
25 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
30 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in developmental tissues, combined with the homology to ribosomal protein s15 of E. coli indicates that the protein product of this gene is  
5 useful for the diagnosis and/or treatment of diseases related to the assembly of ribosomes in the mitochondria, which is important in the translation of RNA into protein. Therefore, this indicates that the protein product of this gene is also useful for the diagnosis and intervention of multiple tumors, as well as in healing wounds, which are thought to be under similar regulation as developmental tissues. Protein, as  
10 well as, antibodies directed against the protein have utility as tumor markers, in addition to immunotherapy targets, for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:122 and may have been publicly available prior to conception  
15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 980 of SEQ ID NO:122, b is an  
20 integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 113**

25

For purposes of this application, this gene and its corresponding translation product are known as the B7-H4 gene and B7-H4 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to embody the following preferred amino acid residues:

30 GIVAFIVFLLIMLIFL (SEQ ID NO: 1236). Polynucleotides encoding this polypeptide are also encompassed by the invention, as are antibodies that bind the polypeptide. The B7-H4 gene shares sequence homology with members of the B7

family of ligands (i.e., B7-1 (See Genbank Accession 507873)). These proteins and their corresponding receptors play vital roles in the growth, differentiation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine

5 production. Therefore, antagonists such as antibodies or small molecules directed against the B7-H4 gene are useful for treating T cell mediated immune system disorders. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention have uses, such as, for example, as a marker in linkage analysis for chromosome 1.

10 The translation product of this gene shares sequence homology with human poliovirus receptor precursors which are thought to be important in viral binding and uptake. The translation product of this gene also shares homology with a mouse member of the immunoglobulin superfamily, which is thought to be important in proper immune function (GENBANK: accession AF061260).

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ELSISISNVALADEGEYTCSIFTMPVRTAKSLVTVLGIPQKPITGYKSSLREKD  
TATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVT  
REDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLL

20 HCEGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCTATSN  
MGSYKAYYTLLNVND (SEQ ID NO:947),

ELSISISNVALADEGEYTCSIFTMPVRTAKSLVTVLGIPQKPITGYKSSLREKD  
TATLNCQSS (SEQ ID NO:948),

CQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVTREDD

25 GASIVCSVNHESL (SEQ ID NO:949),

HESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLHCEGRGNPVPQQY  
LWEKE (SEQ ID NO:950),

WEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCTATSNMGSYKAYYTLLNVND  
(SEQ ID NO:951), PSPVSSSSTYHAIIGGIVAFIVLLLIMLIFLGHY (SEQ ID

30 NO:952), and/or LIRHKGTYLTAEAKGSDDAPDADTAIINAEGGQSGGDDKK  
EYFI (SEQ ID NO:953). Moreover, fragments and variants of these polypeptides

(such as, for example, fragments as described herein, polypeptides at least 80%, 85%,

90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the  
5 invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

A splice variant of this gene has been identified which encodes a polypeptide lacking the following amino acid segment of SEQ ID NO: 361:

DGYWQEQDLELGTLAPLDEAISSTWSSPDMLASQ (SEQ ID NO: 1240). This  
10 splice variant was identified in clone HCB1K47, deposited in ATCC Deposit Accession No. PTA-2574 on October 5, 2000 and in ATCC Deposit Accession No. Unknown on February 16, 2001.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

15 NLSQDGYWQEQDLELGTLAPLDEAISSTWSSPDMLASQDSQP (SEQ ID NO: 1241), DGYWQEQDLELGTLAPLDEAISSTWSSPDMLASQ (SEQ ID NO: 1240), and/or NLSQDSQP (SEQ ID NO: 1242). In a further specific embodiment, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:  
20 MGAPAASLLLLLLFACCWAPGGANLSQDDSQPWTSDETVVAGGTVVLKCCQ VKDHEDSSLQWS (SEQ ID NO: 1243). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
25 conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed almost exclusively in human  
30 brain tissue.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve,

thirteen, fourteen, fifteen, sixteen, or all sixteen of the immunogenic epitopes of the extracellular portion of the B7-H4 protein shown in SEQ ID NO: 361 as residues: Leu-26 to Asp-36, Gln-63 to Asp-71, Lys-87 to Gln-102, Gly-107 to Arg-116, Tyr-172 to Ala-182, Thr-198 to His-207, Glu-209 to Lys-220, Thr-233 to Gly-238, Glu-248 to Gln-259, Pro-273 to Gln-282, Glu-289 to Gln-297, Asn-324 to Thr-330, Val-350 to Pro-355, Ile-390 to Thr-395, Ala-401 to Ala-410, Glu-418 to Tyr-430.

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides.

In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, one or more of the following amino acid sequences:

1.) The extracellular domain of the B7-H4 protein:

MGAPAASLLLLLLFACCWAPGGANLSQDGYWQEQDLELGLTAPLDEAISST  
WSSPDMLASQDSQPWTSDET VVAGGT VVLKCQVKDHEDSSLQWSNPAQQT  
LYFG EKRALRDNR IQLVTSTPHEL SISISNVALADEGEYTC SIFTMPVRTAKSL  
VTVLGIPQKPITGYKSSLREKDTATLNCQSSGSKPAARLTWRKGDQELHGEP  
TRI QEDPNGKTFTVSSSVTFQVTREDDGASIVCSVNHESLKGADRSTSQR IEVL  
YTPTAMIRPDPPHPREGQKLLHCEGRGNPVPQQYLWEKEGSVPPLKMTQES  
ALIFPFLNKSDSGTYGCTATSNMGSYKAYYTLNVNDPSPVPSSSSTYHAIIG  
(SEQ ID NO: 1237);

2.) The mature extracellular domain of the B7-H4 protein:

NLSQDGYWQEQDLELGLTAPLDEAISSTVWSSPDMLASQDSQPWTSDET VV  
AGGT VVLKCQVKDHEDSSLQWSNPAQQTLYFG EKRALRDNR IQLVTSTPHEL  
SISISNVALADEGEYTC SIFTMPVRTAKSLVTVLGIPQKPITGYKSSLREKDTA  
TLNCQSSGSKPAARLTWRKGDQELHGEPTRI QEDPNGKTFTVSSSVTFQVTRE  
DDGASIVCSVNHESLKGADRSTSQR IEVLYTPTAMIRPDPPHPREGQKLLHCE  
EGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCTATSNMG  
SYKAYYTLNVNDPSPVPSSSSTYHAIIG (SEQ ID NO: 1238); and/or

3.) The anticipated leader sequence of the B7-H4 protein:

MGAPAASLLLLLLFACCWAPGGA (SEQ ID NO: 1239).

Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides.



Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H4 protein demonstrating functional activity (SEQ ID NO: 361). Polynucleotides encoding these polypeptides are also encompassed by the invention. By functional activity is meant, a polypeptide  
5 fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H4 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H4 polypeptide for binding) to an anti-B7-H4 antibody],  
10 immunogenicity (ability to generate antibody which binds to a B7-H4 polypeptide), ability to form multimers with B7-H4 polypeptides of the invention, and ability to bind to a receptor or ligand for a B7-H4 polypeptide.

Figures 3A-C show the nucleotide (SEQ ID NO: 123) and deduced amino acid sequence (SEQ ID NO: 361) corresponding to this gene.

15 Figure 4 shows an analysis of the amino acid sequence (SEQ ID NO: 361). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the  
20 highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 4 are also represented in tabular form in Table 4.  
25 The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figures 3A-3C, and Table 4: "Res": amino acid residue of SEQ ID NO: 361 and Figures 3A-3C; "Position": position of the corresponding residue within SEQ ID NO: 361 and Figures 3A-3C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-

Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

5 Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, 10 alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 4 and/or Table 4, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. In a preferred embodiment, the data 15 presented in columns VIII, IX, XIII, and XIV of Table 4 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in 20 which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 4, but may, as shown in Table 4, be represented or identified by using tabular representations of the data presented in Figure 4. The DNA\*STAR computer algorithm used to generate 25 Figure 4 (set on the original default parameters) was used to present the data in Figure 4 in a tabular format (See Table 4). The tabular format of the data in Figure 4 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide 30 sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 123, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least

about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 123. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 123. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 123, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxyl terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-432 where m is an integer from 2 to 426, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 361. More in particular, the invention provides

polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: G-2 to I-432; A-3 to I-432; P-4 to I-432; A-5 to I-432; A-6 to I-432; S-7 to I-432; L-8 to I-432; L-9 to I-432; L-10 to I-432; L-11 to I-432; L-12 to I-432; L-13 to I-432; L-14 to I-432; F-15 to I-432; A-16 to I-432; C-17 to I-432; C-18 to I-432; W-19 to I-432; A-20 to I-432; P-21 to I-432; G-22 to I-432; G-23 to I-432; A-24 to I-432; N-25 to I-432; L-26 to I-432; S-27 to I-432; Q-28 to I-432; D-29 to I-432; G-30 to I-432; Y-31 to I-432; W-32 to I-432; Q-33 to I-432; E-34 to I-432; Q-35 to I-432; D-36 to I-432; L-37 to I-432; E-38 to I-432; L-39 to I-432; G-40 to I-432; T-41 to I-432; L-42 to I-432; A-43 to I-432; P-44 to I-432; L-45 to I-432; D-46 to I-432; E-47 to I-432; A-48 to I-432; I-49 to I-432; S-50 to I-432; S-51 to I-432; T-52 to I-432; V-53 to I-432; W-54 to I-432; S-55 to I-432; S-56 to I-432; P-57 to I-432; D-58 to I-432; M-59 to I-432; L-60 to I-432; A-61 to I-432; S-62 to I-432; Q-63 to I-432; D-64 to I-432; S-65 to I-432; Q-66 to I-432; P-67 to I-432; W-68 to I-432; T-69 to I-432; S-70 to I-432; D-71 to I-432; E-72 to I-432; T-73 to I-432; V-74 to I-432; V-75 to I-432; A-76 to I-432; G-77 to I-432; G-78 to I-432; T-79 to I-432; V-80 to I-432; V-81 to I-432; L-82 to I-432; K-83 to I-432; C-84 to I-432; Q-85 to I-432; V-86 to I-432; K-87 to I-432; D-88 to I-432; H-89 to I-432; E-90 to I-432; D-91 to I-432; S-92 to I-432; S-93 to I-432; L-94 to I-432; Q-95 to I-432; W-96 to I-432; S-97 to I-432; N-98 to I-432; P-99 to I-432; A-100 to I-432; Q-101 to I-432; Q-102 to I-432; T-103 to I-432; L-104 to I-432; Y-105 to I-432; F-106 to I-432; G-107 to I-432; E-108 to I-432; K-109 to I-432; R-110 to I-432; A-111 to I-432; L-112 to I-432; R-113 to I-432; D-114 to I-432; N-115 to I-432; R-116 to I-432; I-117 to I-432; Q-118 to I-432; L-119 to I-432; V-120 to I-432; T-121 to I-432; S-122 to I-432; T-123 to I-432; P-124 to I-432; H-125 to I-432; E-126 to I-432; L-127 to I-432; S-128 to I-432; I-129 to I-432; S-130 to I-432; I-131 to I-432; S-132 to I-432; N-133 to I-432; V-134 to I-432; A-135 to I-432; L-136 to I-432; A-137 to I-432; D-138 to I-432; E-139 to I-432; G-140 to I-432; E-141 to I-432; Y-142 to I-432; T-143 to I-432; C-144 to I-432; S-145 to I-432; I-146 to I-432; F-147 to I-432; T-148 to I-432; M-149 to I-432; P-150 to I-432; V-151 to I-432; R-152 to I-432; T-153 to I-432; A-154 to I-432; K-155 to I-432; S-156 to I-432; L-157 to I-432; V-158 to I-432; T-159 to I-432; V-160 to I-432; L-161 to I-432; G-162 to I-432; I-163 to I-432; P-164 to I-432; Q-165 to I-432; K-166 to I-432; P-167 to I-432; I-168 to I-432; I-169 to I-432;

T-170 to I-432; G-171 to I-432; Y-172 to I-432; K-173 to I-432; S-174 to I-432; S-175 to I-432; L-176 to I-432; R-177 to I-432; E-178 to I-432; K-179 to I-432; D-180 to I-432; T-181 to I-432; A-182 to I-432; T-183 to I-432; L-184 to I-432; N-185 to I-432; C-186 to I-432; Q-187 to I-432; S-188 to I-432; S-189 to I-432; G-190 to I-432; 5 S-191 to I-432; K-192 to I-432; P-193 to I-432; A-194 to I-432; A-195 to I-432; R-196 to I-432; L-197 to I-432; T-198 to I-432; W-199 to I-432; R-200 to I-432; K-201 to I-432; G-202 to I-432; D-203 to I-432; Q-204 to I-432; E-205 to I-432; L-206 to I-432; H-207 to I-432; G-208 to I-432; E-209 to I-432; P-210 to I-432; T-211 to I-432; R-212 to I-432; I-213 to I-432; Q-214 to I-432; E-215 to I-432; D-216 to I-432; P-217 to I-432; N-218 to I-432; G-219 to I-432; K-220 to I-432; T-221 to I-432; F-222 to I-432; T-223 to I-432; V-224 to I-432; S-225 to I-432; S-226 to I-432; S-227 to I-432; V-228 to I-432; T-229 to I-432; F-230 to I-432; Q-231 to I-432; V-232 to I-432; T-233 to I-432; R-234 to I-432; E-235 to I-432; D-236 to I-432; D-237 to I-432; G-238 to I-432; A-239 to I-432; S-240 to I-432; I-241 to I-432; V-242 to I-432; C-243 to I-432; S-244 to I-432; V-245 to I-432; N-246 to I-432; H-247 to I-432; E-248 to I-432; S-249 to I-432; L-250 to I-432; K-251 to I-432; G-252 to I-432; A-253 to I-432; D-254 to I-432; R-255 to I-432; S-256 to I-432; T-257 to I-432; S-258 to I-432; Q-259 to I-432; R-260 to I-432; I-261 to I-432; E-262 to I-432; V-263 to I-432; L-264 to I-432; Y-265 to I-432; T-266 to I-432; P-267 to I-432; T-268 to I-432; A-269 to I-432; 15 M-270 to I-432; I-271 to I-432; R-272 to I-432; P-273 to I-432; D-274 to I-432; P-275 to I-432; P-276 to I-432; H-277 to I-432; P-278 to I-432; R-279 to I-432; E-280 to I-432; G-281 to I-432; Q-282 to I-432; K-283 to I-432; L-284 to I-432; L-285 to I-432; L-286 to I-432; H-287 to I-432; C-288 to I-432; E-289 to I-432; G-290 to I-432; R-291 to I-432; G-292 to I-432; N-293 to I-432; P-294 to I-432; V-295 to I-432; P-296 to I-432; Q-297 to I-432; Q-298 to I-432; Y-299 to I-432; L-300 to I-432; W-301 to I-432; E-302 to I-432; K-303 to I-432; E-304 to I-432; G-305 to I-432; S-306 to I-432; V-307 to I-432; P-308 to I-432; P-309 to I-432; L-310 to I-432; K-311 to I-432; M-312 to I-432; T-313 to I-432; Q-314 to I-432; E-315 to I-432; S-316 to I-432; A-317 to I-432; L-318 to I-432; I-319 to I-432; F-320 to I-432; P-321 to I-432; F-322 to I-432; L-323 to I-432; N-324 to I-432; K-325 to I-432; S-326 to I-432; D-327 to I-432; S-328 to I-432; G-329 to I-432; T-330 to I-432; Y-331 to I-432; G-332 to I-432; C-333 to I-432; T-334 to I-432; A-335 to I-432; T-336 to I-432; S-337 to I-432; N-

338 to I-432; M-339 to I-432; G-340 to I-432; S-341 to I-432; Y-342 to I-432; K-343 to I-432; A-344 to I-432; Y-345 to I-432; Y-346 to I-432; T-347 to I-432; L-348 to I-432; N-349 to I-432; V-350 to I-432; N-351 to I-432; D-352 to I-432; P-353 to I-432; S-354 to I-432; P-355 to I-432; V-356 to I-432; P-357 to I-432; S-358 to I-432; S-359 to I-432; S-360 to I-432; S-361 to I-432; T-362 to I-432; Y-363 to I-432; H-364 to I-432; A-365 to I-432; I-366 to I-432; I-367 to I-432; G-368 to I-432; G-369 to I-432; I-370 to I-432; V-371 to I-432; A-372 to I-432; F-373 to I-432; I-374 to I-432; V-375 to I-432; F-376 to I-432; L-377 to I-432; L-378 to I-432; L-379 to I-432; I-380 to I-432; M-381 to I-432; L-382 to I-432; I-383 to I-432; F-384 to I-432; L-385 to I-432; G-386 to I-432; H-387 to I-432; Y-388 to I-432; L-389 to I-432; I-390 to I-432; R-391 to I-432; H-392 to I-432; K-393 to I-432; G-394 to I-432; T-395 to I-432; Y-396 to I-432; L-397 to I-432; T-398 to I-432; H-399 to I-432; E-400 to I-432; A-401 to I-432; K-402 to I-432; G-403 to I-432; S-404 to I-432; D-405 to I-432; D-406 to I-432; A-407 to I-432; P-408 to I-432; D-409 to I-432; A-410 to I-432; D-411 to I-432; T-412 to I-432; A-413 to I-432; I-414 to I-432; I-415 to I-432; N-416 to I-432; A-417 to I-432; E-418 to I-432; G-419 to I-432; G-420 to I-432; Q-421 to I-432; S-422 to I-432; G-423 to I-432; G-424 to I-432; D-425 to I-432; D-426 to I-432; and/or K-427 to I-432 of SEQ ID NO: 361. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

20 Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to F-431; M-1 to Y-430; M-1 to E-429; M-1 to K-428; M-1 to K-427; M-1 to D-426; M-1 to D-425; M-1 to G-424; M-1 to G-423; M-1 to S-422; M-1 to Q-421; M-1 to G-420; M-1 to G-419; M-1 to E-418; M-1 to A-417; M-1 to N-416; M-1 to I-415; M-1 to I-414; M-1 to A-413; M-1 to T-412; M-1 to D-411; M-1 to A-410; M-1 to D-409; M-1 to P-408; M-1 to A-407; M-1 to D-406; M-1 to D-405; M-1 to S-404; M-1 to G-403; M-1 to K-402; M-1 to A-401; M-1 to E-400; M-1 to H-399; M-1 to T-398; M-1 to L-397; M-1 to Y-396; M-1 to T-395; M-1 to G-394; M-1 to K-393; M-1 to H-392; M-1 to R-391; M-1 to I-390; M-1 to L-389; M-1 to Y-388; M-1 to H-387; M-1 to G-386; M-1 to L-385; M-1 to F-384; M-1 to I-383; M-1 to L-382; M-1 to M-381; M-1 to I-380; M-1 to L-379; M-1 to L-378; M-1 to L-377; M-1 to F-376; M-1 to V-375; M-1 to I-374; M-1 to F-373; M-1 to A-

372; M-1 to V-371; M-1 to I-370; M-1 to G-369; M-1 to G-368; M-1 to I-367; M-1 to I-366; M-1 to A-365; M-1 to H-364; M-1 to Y-363; M-1 to T-362; M-1 to S-361; M-1 to S-360; M-1 to S-359; M-1 to S-358; M-1 to P-357; M-1 to V-356; M-1 to P-355; M-1 to S-354; M-1 to P-353; M-1 to D-352; M-1 to N-351; M-1 to V-350; M-1 to N-349; M-1 to L-348; M-1 to T-347; M-1 to Y-346; M-1 to Y-345; M-1 to A-344; M-1 to K-343; M-1 to Y-342; M-1 to S-341; M-1 to G-340; M-1 to M-339; M-1 to N-338; M-1 to S-337; M-1 to T-336; M-1 to A-335; M-1 to T-334; M-1 to C-333; M-1 to G-332; M-1 to Y-331; M-1 to T-330; M-1 to G-329; M-1 to S-328; M-1 to D-327; M-1 to S-326; M-1 to K-325; M-1 to N-324; M-1 to L-323; M-1 to F-322; M-1 to P-321; M-1 to F-320; M-1 to I-319; M-1 to L-318; M-1 to A-317; M-1 to S-316; M-1 to E-315; M-1 to Q-314; M-1 to T-313; M-1 to M-312; M-1 to K-311; M-1 to L-310; M-1 to P-309; M-1 to P-308; M-1 to V-307; M-1 to S-306; M-1 to G-305; M-1 to E-304; M-1 to K-303; M-1 to E-302; M-1 to W-301; M-1 to L-300; M-1 to Y-299; M-1 to Q-298; M-1 to Q-297; M-1 to P-296; M-1 to V-295; M-1 to P-294; M-1 to N-293; M-1 to G-292; M-1 to R-291; M-1 to G-290; M-1 to E-289; M-1 to C-288; M-1 to H-287; M-1 to L-286; M-1 to L-285; M-1 to L-284; M-1 to K-283; M-1 to Q-282; M-1 to G-281; M-1 to E-280; M-1 to R-279; M-1 to P-278; M-1 to H-277; M-1 to P-276; M-1 to P-275; M-1 to D-274; M-1 to P-273; M-1 to R-272; M-1 to I-271; M-1 to M-270; M-1 to A-269; M-1 to T-268; M-1 to P-267; M-1 to T-266; M-1 to Y-265; M-1 to L-264; M-1 to V-263; M-1 to E-262; M-1 to I-261; M-1 to R-260; M-1 to Q-259; M-1 to S-258; M-1 to T-257; M-1 to S-256; M-1 to R-255; M-1 to D-254; M-1 to A-253; M-1 to G-252; M-1 to K-251; M-1 to L-250; M-1 to S-249; M-1 to E-248; M-1 to H-247; M-1 to N-246; M-1 to V-245; M-1 to S-244; M-1 to C-243; M-1 to V-242; M-1 to I-241; M-1 to S-240; M-1 to A-239; M-1 to G-238; M-1 to D-237; M-1 to D-236; M-1 to E-235; M-1 to R-234; M-1 to T-233; M-1 to V-232; M-1 to Q-231; M-1 to F-230; M-1 to T-229; M-1 to V-228; M-1 to S-227; M-1 to S-226; M-1 to S-225; M-1 to V-224; M-1 to T-223; M-1 to F-222; M-1 to T-221; M-1 to K-220; M-1 to G-219; M-1 to N-218; M-1 to P-217; M-1 to D-216; M-1 to E-215; M-1 to Q-214; M-1 to I-213; M-1 to R-212; M-1 to T-211; M-1 to P-210; M-1 to E-209; M-1 to G-208; M-1 to H-207; M-1 to L-206; M-1 to E-205; M-1 to Q-204; M-1 to D-203; M-1 to G-202; M-1 to K-201; M-1 to R-200; M-1 to W-199; M-1 to T-198; M-1 to L-197; M-1 to R-196; M-1 to A-195; M-1 to A-194; M-1 to P-193; M-1 to K-192; M-1 to S-191; M-1

to G-190; M-1 to S-189; M-1 to S-188; M-1 to Q-187; M-1 to C-186; M-1 to N-185;  
M-1 to L-184; M-1 to T-183; M-1 to A-182; M-1 to T-181; M-1 to D-180; M-1 to K-  
179; M-1 to E-178; M-1 to R-177; M-1 to L-176; M-1 to S-175; M-1 to S-174; M-1  
to K-173; M-1 to Y-172; M-1 to G-171; M-1 to T-170; M-1 to I-169; M-1 to I-168;  
5 M-1 to P-167; M-1 to K-166; M-1 to Q-165; M-1 to P-164; M-1 to I-163; M-1 to G-  
162; M-1 to L-161; M-1 to V-160; M-1 to T-159; M-1 to V-158; M-1 to L-157; M-1  
to S-156; M-1 to K-155; M-1 to A-154; M-1 to T-153; M-1 to R-152; M-1 to V-151;  
M-1 to P-150; M-1 to M-149; M-1 to T-148; M-1 to F-147; M-1 to I-146; M-1 to S-  
145; M-1 to C-144; M-1 to T-143; M-1 to Y-142; M-1 to E-141; M-1 to G-140; M-1  
10 to E-139; M-1 to D-138; M-1 to A-137; M-1 to L-136; M-1 to A-135; M-1 to V-134;  
M-1 to N-133; M-1 to S-132; M-1 to I-131; M-1 to S-130; M-1 to I-129; M-1 to S-  
128; M-1 to L-127; M-1 to E-126; M-1 to H-125; M-1 to P-124; M-1 to T-123; M-1  
to S-122; M-1 to T-121; M-1 to V-120; M-1 to L-119; M-1 to Q-118; M-1 to I-117;  
M-1 to R-116; M-1 to N-115; M-1 to D-114; M-1 to R-113; M-1 to L-112; M-1 to A-  
15 111; M-1 to R-110; M-1 to K-109; M-1 to E-108; M-1 to G-107; M-1 to F-106; M-1  
to Y-105; M-1 to L-104; M-1 to T-103; M-1 to Q-102; M-1 to Q-101; M-1 to A-100;  
M-1 to P-99; M-1 to N-98; M-1 to S-97; M-1 to W-96; M-1 to Q-95; M-1 to L-94; M-  
1 to S-93; M-1 to S-92; M-1 to D-91; M-1 to E-90; M-1 to H-89; M-1 to D-88; M-1  
to K-87; M-1 to V-86; M-1 to Q-85; M-1 to C-84; M-1 to K-83; M-1 to L-82; M-1 to  
20 V-81; M-1 to V-80; M-1 to T-79; M-1 to G-78; M-1 to G-77; M-1 to A-76; M-1 to V-  
75; M-1 to V-74; M-1 to T-73; M-1 to E-72; M-1 to D-71; M-1 to S-70; M-1 to T-69;  
M-1 to W-68; M-1 to P-67; M-1 to Q-66; M-1 to S-65; M-1 to D-64; M-1 to Q-63;  
M-1 to S-62; M-1 to A-61; M-1 to L-60; M-1 to M-59; M-1 to D-58; M-1 to P-57; M-  
1 to S-56; M-1 to S-55; M-1 to W-54; M-1 to V-53; M-1 to T-52; M-1 to S-51; M-1  
25 to S-50; M-1 to I-49; M-1 to A-48; M-1 to E-47; M-1 to D-46; M-1 to L-45; M-1 to  
P-44; M-1 to A-43; M-1 to L-42; M-1 to T-41; M-1 to G-40; M-1 to L-39; M-1 to E-  
38; M-1 to L-37; M-1 to D-36; M-1 to Q-35; M-1 to E-34; M-1 to Q-33; M-1 to W-  
32; M-1 to Y-31; M-1 to G-30; M-1 to D-29; M-1 to Q-28; M-1 to S-27; M-1 to L-26;  
M-1 to N-25; M-1 to A-24; M-1 to G-23; M-1 to G-22; M-1 to P-21; M-1 to A-20; M-  
30 1 to W-19; M-1 to C-18; M-1 to C-17; M-1 to A-16; M-1 to F-15; M-1 to L-14; M-1  
to L-13; M-1 to L-12; M-1 to L-11; M-1 to L-10; M-1 to L-9; M-1 to L-8; and/or M-1



to S-7 of SEQ ID NO: 361. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response. Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxyl terminus of the amino acid sequence of the polypeptide shown in Figures 3A-3C (SEQ ID NO: 361), as described by the general formula 1-n, where n is an integer from 6 to 432, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 361.

More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H4 protein (SEQ ID NO: 1238): L-26 to G-368; S-27 to G-368; Q-28 to G-368; D-29 to G-368; G-30 to G-368; Y-31 to G-368; W-32 to G-368; Q-33 to G-368; E-34 to G-368; Q-35 to G-368; D-36 to G-368; L-37 to G-368; E-38 to G-368; L-39 to G-368; G-40 to G-368; T-41 to G-368; L-42 to G-368; A-43 to G-368; P-44 to G-368; L-45 to G-368; D-46 to G-368; E-47 to G-368; A-48 to G-368; I-49 to G-368; S-50 to G-368; S-51 to G-368; T-52 to G-368; V-53 to G-368; W-54 to G-368; S-55 to G-368; S-56 to G-368; P-57 to G-368; D-58 to G-368; M-59 to G-368; L-60 to G-

368; A-61 to G-368; S-62 to G-368; Q-63 to G-368; D-64 to G-368; S-65 to G-368;  
Q-66 to G-368; P-67 to G-368; W-68 to G-368; T-69 to G-368; S-70 to G-368; D-71  
to G-368; E-72 to G-368; T-73 to G-368; V-74 to G-368; V-75 to G-368; A-76 to G-  
368; G-77 to G-368; G-78 to G-368; T-79 to G-368; V-80 to G-368; V-81 to G-368;  
5 L-82 to G-368; K-83 to G-368; C-84 to G-368; Q-85 to G-368; V-86 to G-368; K-87  
to G-368; D-88 to G-368; H-89 to G-368; E-90 to G-368; D-91 to G-368; S-92 to G-  
368; S-93 to G-368; L-94 to G-368; Q-95 to G-368; W-96 to G-368; S-97 to G-368;  
N-98 to G-368; P-99 to G-368; A-100 to G-368; Q-101 to G-368; Q-102 to G-368; T-  
103 to G-368; L-104 to G-368; Y-105 to G-368; F-106 to G-368; G-107 to G-368; E-  
10 108 to G-368; K-109 to G-368; R-110 to G-368; A-111 to G-368; L-112 to G-368; R-  
113 to G-368; D-114 to G-368; N-115 to G-368; R-116 to G-368; I-117 to G-368; Q-  
118 to G-368; L-119 to G-368; V-120 to G-368; T-121 to G-368; S-122 to G-368; T-  
123 to G-368; P-124 to G-368; H-125 to G-368; E-126 to G-368; L-127 to G-368; S-  
128 to G-368; I-129 to G-368; S-130 to G-368; I-131 to G-368; S-132 to G-368; N-  
15 133 to G-368; V-134 to G-368; A-135 to G-368; L-136 to G-368; A-137 to G-368; D-  
138 to G-368; E-139 to G-368; G-140 to G-368; E-141 to G-368; Y-142 to G-368; T-  
143 to G-368; C-144 to G-368; S-145 to G-368; I-146 to G-368; F-147 to G-368; T-  
148 to G-368; M-149 to G-368; P-150 to G-368; V-151 to G-368; R-152 to G-368; T-  
153 to G-368; A-154 to G-368; K-155 to G-368; S-156 to G-368; L-157 to G-368; V-  
20 158 to G-368; T-159 to G-368; V-160 to G-368; L-161 to G-368; G-162 to G-368; I-  
163 to G-368; P-164 to G-368; Q-165 to G-368; K-166 to G-368; P-167 to G-368; I-  
168 to G-368; I-169 to G-368; T-170 to G-368; G-171 to G-368; Y-172 to G-368; K-  
173 to G-368; S-174 to G-368; S-175 to G-368; L-176 to G-368; R-177 to G-368; E-  
178 to G-368; K-179 to G-368; D-180 to G-368; T-181 to G-368; A-182 to G-368; T-  
25 183 to G-368; L-184 to G-368; N-185 to G-368; C-186 to G-368; Q-187 to G-368; S-  
188 to G-368; S-189 to G-368; G-190 to G-368; S-191 to G-368; K-192 to G-368; P-  
193 to G-368; A-194 to G-368; A-195 to G-368; R-196 to G-368; L-197 to G-368; T-  
198 to G-368; W-199 to G-368; R-200 to G-368; K-201 to G-368; G-202 to G-368;  
D-203 to G-368; Q-204 to G-368; E-205 to G-368; L-206 to G-368; H-207 to G-368;  
30 G-208 to G-368; E-209 to G-368; P-210 to G-368; T-211 to G-368; R-212 to G-368;  
I-213 to G-368; Q-214 to G-368; E-215 to G-368; D-216 to G-368; P-217 to G-368;  
N-218 to G-368; G-219 to G-368; K-220 to G-368; T-221 to G-368; F-222 to G-368;

T-223 to G-368; V-224 to G-368; S-225 to G-368; S-226 to G-368; S-227 to G-368;  
 V-228 to G-368; T-229 to G-368; F-230 to G-368; Q-231 to G-368; V-232 to G-368;  
 T-233 to G-368; R-234 to G-368; E-235 to G-368; D-236 to G-368; D-237 to G-368;  
 G-238 to G-368; A-239 to G-368; S-240 to G-368; I-241 to G-368; V-242 to G-368;  
 5 C-243 to G-368; S-244 to G-368; V-245 to G-368; N-246 to G-368; H-247 to G-368;  
 E-248 to G-368; S-249 to G-368; L-250 to G-368; K-251 to G-368; G-252 to G-368;  
 A-253 to G-368; D-254 to G-368; R-255 to G-368; S-256 to G-368; T-257 to G-368;  
 S-258 to G-368; Q-259 to G-368; R-260 to G-368; I-261 to G-368; E-262 to G-368;  
 V-263 to G-368; L-264 to G-368; Y-265 to G-368; T-266 to G-368; P-267 to G-368;  
 10 T-268 to G-368; A-269 to G-368; M-270 to G-368; I-271 to G-368; R-272 to G-368;  
 P-273 to G-368; D-274 to G-368; P-275 to G-368; P-276 to G-368; H-277 to G-368;  
 P-278 to G-368; R-279 to G-368; E-280 to G-368; G-281 to G-368; Q-282 to G-368;  
 K-283 to G-368; L-284 to G-368; L-285 to G-368; L-286 to G-368; H-287 to G-368;  
 C-288 to G-368; E-289 to G-368; G-290 to G-368; R-291 to G-368; G-292 to G-368;  
 15 N-293 to G-368; P-294 to G-368; V-295 to G-368; P-296 to G-368; Q-297 to G-368;  
 Q-298 to G-368; Y-299 to G-368; L-300 to G-368; W-301 to G-368; E-302 to G-368;  
 K-303 to G-368; E-304 to G-368; G-305 to G-368; S-306 to G-368; V-307 to G-368;  
 P-308 to G-368; P-309 to G-368; L-310 to G-368; K-311 to G-368; M-312 to G-368;  
 T-313 to G-368; Q-314 to G-368; E-315 to G-368; S-316 to G-368; A-317 to G-368;  
 20 L-318 to G-368; I-319 to G-368; F-320 to G-368; P-321 to G-368; F-322 to G-368; L-  
 323 to G-368; N-324 to G-368; K-325 to G-368; S-326 to G-368; D-327 to G-368; S-  
 328 to G-368; G-329 to G-368; T-330 to G-368; Y-331 to G-368; G-332 to G-368; C-  
 333 to G-368; T-334 to G-368; A-335 to G-368; T-336 to G-368; S-337 to G-368; N-  
 338 to G-368; M-339 to G-368; G-340 to G-368; S-341 to G-368; Y-342 to G-368;  
 25 K-343 to G-368; A-344 to G-368; Y-345 to G-368; Y-346 to G-368; T-347 to G-368;  
 L-348 to G-368; N-349 to G-368; V-350 to G-368; N-351 to G-368; D-352 to G-368;  
 P-353 to G-368; S-354 to G-368; P-355 to G-368; V-356 to G-368; P-357 to G-368;  
 S-358 to G-368; S-359 to G-368; S-360 to G-368; S-361 to G-368; T-362 to G-368;  
 and/or Y-363 to G-368 of SEQ ID NO: 1238. Polypeptides encoded by these  
 30 polynucleotides are also encompassed by the invention.

Additionally, the invention provides polynucleotides encoding polypeptides  
 comprising, or alternatively consisting of, an amino acid sequence selected from the

group of C-terminal deletions of the mature extracellular portion of the B7-H4 protein (SEQ ID NO: 1238): N-25 to I-367; N-25 to I-366; N-25 to A-365; N-25 to H-364; N-25 to Y-363; N-25 to T-362; N-25 to S-361; N-25 to S-360; N-25 to S-359; N-25 to S-358; N-25 to P-357; N-25 to V-356; N-25 to P-355; N-25 to S-354; N-25 to P-353; 5 N-25 to D-352; N-25 to N-351; N-25 to V-350; N-25 to N-349; N-25 to L-348; N-25 to T-347; N-25 to Y-346; N-25 to Y-345; N-25 to A-344; N-25 to K-343; N-25 to Y-342; N-25 to S-341; N-25 to G-340; N-25 to M-339; N-25 to N-338; N-25 to S-337; N-25 to T-336; N-25 to A-335; N-25 to T-334; N-25 to C-333; N-25 to G-332; N-25 to Y-331; N-25 to T-330; N-25 to G-329; N-25 to S-328; N-25 to D-327; N-25 to S-10 326; N-25 to K-325; N-25 to N-324; N-25 to L-323; N-25 to F-322; N-25 to P-321; N-25 to F-320; N-25 to I-319; N-25 to L-318; N-25 to A-317; N-25 to S-316; N-25 to E-315; N-25 to Q-314; N-25 to T-313; N-25 to M-312; N-25 to K-311; N-25 to L-310; N-25 to P-309; N-25 to P-308; N-25 to V-307; N-25 to S-306; N-25 to G-305; N-25 to E-304; N-25 to K-303; N-25 to E-302; N-25 to W-301; N-25 to L-300; N-25 15 to Y-299; N-25 to Q-298; N-25 to Q-297; N-25 to P-296; N-25 to V-295; N-25 to P-294; N-25 to N-293; N-25 to G-292; N-25 to R-291; N-25 to G-290; N-25 to E-289; N-25 to C-288; N-25 to H-287; N-25 to L-286; N-25 to L-285; N-25 to L-284; N-25 to K-283; N-25 to Q-282; N-25 to G-281; N-25 to E-280; N-25 to R-279; N-25 to P-278; N-25 to H-277; N-25 to P-276; N-25 to P-275; N-25 to D-274; N-25 to P-273; 20 N-25 to R-272; N-25 to I-271; N-25 to M-270; N-25 to A-269; N-25 to T-268; N-25 to P-267; N-25 to T-266; N-25 to Y-265; N-25 to L-264; N-25 to V-263; N-25 to E-262; N-25 to I-261; N-25 to R-260; N-25 to Q-259; N-25 to S-258; N-25 to T-257; N-25 to S-256; N-25 to R-255; N-25 to D-254; N-25 to A-253; N-25 to G-252; N-25 to K-251; N-25 to L-250; N-25 to S-249; N-25 to E-248; N-25 to H-247; N-25 to N-246; 25 N-25 to V-245; N-25 to S-244; N-25 to C-243; N-25 to V-242; N-25 to I-241; N-25 to S-240; N-25 to A-239; N-25 to G-238; N-25 to D-237; N-25 to D-236; N-25 to E-235; N-25 to R-234; N-25 to T-233; N-25 to V-232; N-25 to Q-231; N-25 to F-230; N-25 to T-229; N-25 to V-228; N-25 to S-227; N-25 to S-226; N-25 to S-225; N-25 to V-224; N-25 to T-223; N-25 to F-222; N-25 to T-221; N-25 to K-220; N-25 to G-219; 30 N-25 to N-218; N-25 to P-217; N-25 to D-216; N-25 to E-215; N-25 to Q-214; N-25 to I-213; N-25 to R-212; N-25 to T-211; N-25 to P-210; N-25 to E-209; N-25 to G-208; N-25 to H-207; N-25 to L-206; N-25 to E-205; N-25 to Q-204; N-25 to D-203;

N-25 to G-202; N-25 to K-201; N-25 to R-200; N-25 to W-199; N-25 to T-198; N-25 to L-197; N-25 to R-196; N-25 to A-195; N-25 to A-194; N-25 to P-193; N-25 to K-192; N-25 to S-191; N-25 to G-190; N-25 to S-189; N-25 to S-188; N-25 to Q-187; N-25 to C-186; N-25 to N-185; N-25 to L-184; N-25 to T-183; N-25 to A-182; N-25 to T-181; N-25 to D-180; N-25 to K-179; N-25 to E-178; N-25 to R-177; N-25 to L-176; N-25 to S-175; N-25 to S-174; N-25 to K-173; N-25 to Y-172; N-25 to G-171; N-25 to T-170; N-25 to I-169; N-25 to I-168; N-25 to P-167; N-25 to K-166; N-25 to Q-165; N-25 to P-164; N-25 to I-163; N-25 to G-162; N-25 to L-161; N-25 to V-160; N-25 to T-159; N-25 to V-158; N-25 to L-157; N-25 to S-156; N-25 to K-155; N-25 to A-154; N-25 to T-153; N-25 to R-152; N-25 to V-151; N-25 to P-150; N-25 to M-149; N-25 to T-148; N-25 to F-147; N-25 to I-146; N-25 to S-145; N-25 to C-144; N-25 to T-143; N-25 to Y-142; N-25 to E-141; N-25 to G-140; N-25 to E-139; N-25 to D-138; N-25 to A-137; N-25 to L-136; N-25 to A-135; N-25 to V-134; N-25 to N-133; N-25 to S-132; N-25 to I-131; N-25 to S-130; N-25 to I-129; N-25 to S-128; N-25 to L-127; N-25 to E-126; N-25 to H-125; N-25 to P-124; N-25 to T-123; N-25 to S-122; N-25 to T-121; N-25 to V-120; N-25 to L-119; N-25 to Q-118; N-25 to I-117; N-25 to R-116; N-25 to N-115; N-25 to D-114; N-25 to R-113; N-25 to L-112; N-25 to A-111; N-25 to R-110; N-25 to K-109; N-25 to E-108; N-25 to G-107; N-25 to F-106; N-25 to Y-105; N-25 to L-104; N-25 to T-103; N-25 to Q-102; N-25 to Q-101; N-25 to A-100; N-25 to P-99; N-25 to N-98; N-25 to S-97; N-25 to W-96; N-25 to Q-95; N-25 to L-94; N-25 to S-93; N-25 to S-92; N-25 to D-91; N-25 to E-90; N-25 to H-89; N-25 to D-88; N-25 to K-87; N-25 to V-86; N-25 to Q-85; N-25 to C-84; N-25 to K-83; N-25 to L-82; N-25 to V-81; N-25 to V-80; N-25 to T-79; N-25 to G-78; N-25 to G-77; N-25 to A-76; N-25 to V-75; N-25 to V-74; N-25 to T-73; N-25 to E-72; N-25 to D-71; N-25 to S-70; N-25 to T-69; N-25 to W-68; N-25 to P-67; N-25 to Q-66; N-25 to S-65; N-25 to D-64; N-25 to Q-63; N-25 to S-62; N-25 to A-61; N-25 to L-60; N-25 to M-59; N-25 to D-58; N-25 to P-57; N-25 to S-56; N-25 to S-55; N-25 to W-54; N-25 to V-53; N-25 to T-52; N-25 to S-51; N-25 to S-50; N-25 to I-49; N-25 to A-48; N-25 to E-47; N-25 to D-46; N-25 to L-45; N-25 to P-44; N-25 to A-43; N-25 to L-42; N-25 to T-41; N-25 to G-40; N-25 to L-39; N-25 to E-38; N-25 to L-37; N-25 to D-36; N-25 to Q-35; N-25 to E-34; N-25 to Q-33; N-25 to W-32; and/or

N-25 to Y-31 of SEQ ID NO: 1238. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also  
5 provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 361, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid  
15 sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit Nos. 209007 (deposited on April 28, 1997) and 209083  
20 (deposited on May 29, 1997), where this portion excludes any integer of amino acid residues from 1 to about 228 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit Nos. 209007 and 209083, or any integer of amino acid residues from 1 to about 228 amino acids from the carboxyl terminus, or any combination of the above amino terminal  
25 and carboxyl terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Nos. 209007 and 209083. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers  
30 in chromosome identification, chromosome mapping, and linkage analysis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of CNS and/or immune system tissue(s) or cell type(s)

present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells and/or neutrophils, susceptibility to viral disease and diseases of the CNS, especially cancers of that system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H4 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activities as are disclosed herein (e.g., T cell modulated activities).

For a number of disorders of the above tissues or cells, particularly of the immune system and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The homology to members of the B7 family of ligands indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells and/or neutrophils. In particular, the translation product of the B7-H4 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines.

More generally, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as

an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood  
5 lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

The tissue distribution and homology to poliovirus receptor precursors  
10 suggests that the protein product of this clone would be useful for the treatment and prevention of diseases that involve the binding and uptake of virus particles for infection. It might also be helpful in genetic therapy where the goal is to insert foreign DNA into infected cells. With the help of this protein, the binding and uptake of this foreign DNA might be aided. In addition, it is expected that over expression of  
15 this gene will indicate abnormalities involving the CNS, particularly cancers of that system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
20 related to SEQ ID NO: 123 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence  
25 described by the general formula of a-b, where a is any integer between 1 to 2523 of SEQ ID NO: 123, b is an integer of 15 to 2537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 123

30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 114**



The translation product of this gene shares sequence homology with YO87\_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* in addition to alpha-1 collagen type III (See Genbank Accession No. gi|537432). In specific embodiments, polypeptides of the invention comprise, or alternatively

5 consists of, an amino acid sequence selected from the group:

VPPELPDRVHQLHQA VQGCA LGRPGFPGGP THSGHHKSHPGPAGGDYNRCDR  
PGQVHLHNPRGTGRRGQLHPTAGPGVHRRACPSQQLPHRLGPGVPCPSPSLT  
PVLPSWTQSWCGLPGYTSSS (SEQ ID NO:954),

VHQLHQA VQGCA LGRPGFPGGP (SEQ ID NO:955),

10 PTHSGHHKSHPGPAGGDYNRCDRPGQVHLHNPRGTGRRGQLH (SEQ ID  
NO:956), and/or

LHPTAGPGVHRRACPSQQLPHRLGPGVPCPSPSLTPVLPSWTQSWCGLPGYTS  
SS (SEQ ID NO:957). Moreover, fragments and variants of these polypeptides (such

as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
15 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides ) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the  
invention. Polynucleotides encoding these polypeptides are also encompassed by the  
20 invention.

This gene is expressed primarily in brain cells, and to a lesser extent in  
activated B and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
25 and for diagnosis of diseases and conditions which include, but are not limited to,  
neurodegeneration and immunological disorders. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of  
disorders of the above tissues or cells, particularly of the neural and immune systems,  
30 expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues or cell types (e.g. brain, immune, cancerous and wounded  
tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

- 5 NO: 362 as residues: Glu-34 to Glu-39, Gly-51 to Ser-72, Ala-88 to Glu-93, Gln-100 to Val-105.

The tissue distribution in brain cells, combined with the homology to YO87\_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* as well as to a conserved alpha-1 collagen type III protein indicates that the protein product of this gene is useful for the detection and treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:124 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1376 of SEQ ID NO:124, b is an integer of 15 to 1390, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 115

The translation product of this gene shares sequence homology with alpha 3 type IX collagen, which is thought to be important in hyaline cartilage formation via its ability to uptake inorganic sulfate by cells (See Genbank Accession No. gi|975657).

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- SLRRPRSAAXQTLTTLSSVSSASSSALPGSREPCDPRAPPPRSGSAASCCSCC  
 CSCPRRRAPLRSPRGSKRRIRQREVVDLYNGMCLQGPAGVPGRDGSPGANGI  
 PGTPGIPGRDGFKEGKEGCLRESFEESWTPNYKQCSWSSLNYGIDLGKIAECT  
 10 FTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAEC SGPLPIEAIYLDQ  
 GSPEMNSTINIHR TSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNS  
 VSRIII EELPK (SEQ ID NO:958),  
 SLRRPRSAAXQTLTTLSSVSSASSSALPGSREPCDPRAPPPRSGSAASCCSCC  
 CSCPRR (SEQ ID NO:959),  
 15 RAPLRSPRGSKRRIRQREVVDLYNGMCLQGPAGVPGRDGSPGANGIPGTPGI  
 (SEQ ID NO:960),  
 TPGIPGRDGFKEGKEGCLRESFEESWTPNYKQCSWSSLNYGIDLGKIAECTF  
 (SEQ ID NO:961),  
 FTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAEC SGPLPIEAIYLDQ  
 20 GSPEMNSTINIHR (SEQ ID NO:962), and/or  
 RTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIII EELPK  
 (SEQ ID NO:963). Moreover, fragments and variants of these polypeptides (such as,  
 for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
 25 encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
 polynucleotide encoding these polypeptides ) are encompassed by the invention.  
 Antibodies that bind polypeptides of the invention are also encompassed by the  
 invention. Polynucleotides encoding these polypeptides are also encompassed by the  
 invention.  
 30 This gene is expressed primarily in smooth muscle, and to a lesser extent in  
 synovial tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, dwarfism, spinal deformation, and specific joint abnormalities as well as

5 chondrodysplasias, i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid and autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. muscle, synovial tissues, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard

15 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in smooth muscle, and homology to alpha 3 type IX collagen indicates that the protein product of this gene is useful for the treatment and diagnosis of diseases associated with the mutation in this gene which leads to the

20 many different types of chondrodysplasias. By the use of this product, the abnormal growth and development of bones of the limbs and spine could be detected or treated *in utero*, since the protein or polypeptides thereof could affect epithelial cells early in development, and later the chondrocytes of the developing craniofacial structure. In addition, the expression of this gene product in synovium would suggest a role in the

25 detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and

30 specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Moreover, the expression within smooth muscle

indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to, atherosclerosis, embolism, stroke, aneurysm, or microvascular disease. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:125 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1274 of SEQ ID NO:125, b is an integer of 15 to 1288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 116**

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase, which is thought to be important in viral replication.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
TKKENCRPASLMNIDTKILNKILMNQ (SEQ ID NO:964). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are

also encompassed by the invention. (See Genbank Accession No. pir|A25313|GNHUL1).

This gene is expressed primarily in human meningioma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, retroviral diseases such as AIDS, and possibly certain cancers due to transactivation of latent cell division genes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. meningioma, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human meningioma, combined with the homology to a retrovirus-related reverse transcriptase indicates that the protein product of this gene is useful for the detection and treatment of diseases and conditions associated with retroviral infection, since a functional reverse transcriptase (RT) or RT-like molecule is an integral component of the retroviral life cycle. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:126 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1503 of SEQ ID NO:126, b is an

integer of 15 to 1517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 117

The translation product of this gene shares sequence homology with an unknown gene from *C. elegans*, as well as weak homolog with mammalian metaxin, a gene contiguous to both thrombospondin 3 and glucocerebrosidase, and is known to

10 be required for embryonic development. Recently another group cloned and sequenced this gene from humans, naming it metaxin 2. It is thought that metaxin 1 and metaxin 2 interact, and are associated with the mammalian mitochondrial outer membrane (See Genbank Accession No. AF053551).

In specific embodiments, polypeptides of the invention comprise, or alternatively

15 consists of, an amino acid sequence selected from the group:

MCNLPIKVVCRAAEYMSPSGKVPXXHVGNGVQVSELGPIVQFVKAKGHSLS  
DGLEEVQKAEMKAYMELVNNMLLTAEYLQWCDEATVGXITHXRYGSPYP  
WPLXHLAYQKQWEVKRKXKAIGWGKKTLQVLEDVDQCCQALSQRLGTQ  
PYFFNKQPTELDALVFGHLYTILTTQLTNDELSEKVKNYSNLLAFCRRIEQHY

20 FED RGKGRLS (SEQ ID NO:965),  
MCNLPIKVVCRAAEYMSPSGKVPXXHVGNGVQVSELGPIVQFVK (SEQ ID  
NO:966), FVKAKGHSLSDGLEEVQKAEMKAYMELVNNMLLTAEYLQWCDE  
(SEQ ID NO:967), LQWCDEATVGXITHXRYGSPYPWP  
LXHLAYQKQWEVKRKXKAIGWGKKTL (SEQ ID NO:968),

25 DQVLEDVDQCCQ ALSQRLGTQPYFFNKQPTELDALVFGHLYTI (SEQ ID  
NO:969), and/or LTTQLTNDELSEKVKNYSNLLAFCRRIEQHYFEDRGKGRLS  
(SEQ ID NO:970). Moreover, fragments and variants of these polypeptides (such as,  
for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides

30 encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides ) are encompassed by the invention.  
Antibodies that bind polypeptides of the invention are also encompassed by the

invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. gi|1326108).

The gene encoding the disclosed cDNA is thought to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in  
5 linkage analysis for chromosome 2.

This gene is expressed primarily in fetal tissues, and to a lesser extent in hematopoietic cells and tissues, including spleen, monocytes, and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
10 and for diagnosis of diseases and conditions which include, but are not limited to, cancer; lymphoproliferative disorders; inflammation; chondrosarcoma, and Gaucher disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
15 particularly of the hematopoietic and embryonic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, fetal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of cancer and other proliferative disorders. Moreover, this protein may play a role in the regulation of cellular  
25 division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and survival of hematopoietic cell lineages. Thus, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor  
30 cells. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:127 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1059 of SEQ ID NO:127, b is an integer of 15 to 1073, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 118

The translation product of this gene shares sequence homology with reverse transcriptase, which is important in the synthesis of a cDNA chain from an RNA molecule, and is a method whereby the infecting RNA chains of retroviruses are transcribed into their DNA complements.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MXXXNSHITFTLNVNGLNAPNERHRLANWIQSQDQVCCIQETHLTGRDTHR  
 LKIKGWRKIYQANGKQKK (SEQ ID NO:971),  
 FTLNVNGLNAPNERHRLANWIQSQDQVC (SEQ ID NO:972),  
 THLTGRDTHRLKIKGWR (SEQ ID NO:973), and/or GWRKIYQANGKQKK  
 (SEQ ID NO:974). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. gi|2072964).

This gene is expressed primarily in skin, and to a lesser extent in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, 5 cancers; hematopoietic disorders; inflammation; disorders of immune surveillance. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermis and/or hematopoietic system, expression of this gene at significantly higher 10 or lower levels may be routinely detected in certain tissues or cell types (e.g. skin, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not 15 having the disorder.

The tissue distribution in skin, combined with the homology to a reverse transcriptase indicates that the protein product of this gene is useful for cancer therapy, particularly of the integumentary system. Expression in the skin also indicates that this gene is useful in wound healing and fibrosis. Expression by 20 neutrophils also indicates that this gene product plays a role in inflammation and the control of immune surveillance (i.e., recognition of viral pathogens). Reverse transcriptase family members are also useful in the detection and treatment of AIDS. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:128 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is 30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 286 of SEQ ID NO:128, b is an

integer of 15 to 300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 119

The translation product of this gene shares sequence homology with reverse transcriptase, which is important in the synthesis of a cDNA copy of an RNA molecule, and is a method whereby a retrovirus reverse-transcribes its genome into an inheritable DNA copy.

This gene is expressed primarily in the frontal cortex of brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the frontal cortex, combined with the homology to a reverse transcriptase suggest that this gene is useful in the treatment of cancer and AIDS, particularly of the neural system. The expression in brain indicates that it plays a role in neurodegenerative disorders and in neural degeneration. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of

such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:129 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1261 of SEQ ID NO:129, b is an integer of 15 to 1275; where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 120

The translation product of this gene shares homology to a hypothetical protein in *Schizosaccharomyces pombe* (See Genbank Accession No. 2281980).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: IYHLHSWIFFHFKRAFCMCFITMKVIHAHCSKLRKCXNAQIS VFCTTLTASYPT (SEQ ID NO:975), IYHLHSWIFFHFKRAFCMCFITM (SEQ ID NO:976), and/or KVIHAHCSKLRKCXNAQISVFCTTLTASYPT (SEQ ID NO:977). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 18. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

5 This gene is expressed primarily in adult hypothalamus and to a lesser extent in infant brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; endocrine function; and vertigo. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution in adult hypothalamus and infant brain indicates that the protein product of this gene is useful for the treatment and diagnosis of neurodegenerative disorders; diagnosis of tumors of a brain or neuronal origin; treatments involving hormonal control of the entire body and of homeostasis, behavioral disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:130 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 458 of SEQ ID NO:130, b is an integer of 15 to 472, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 121

10

The translation product of this gene shares sequence homology with the human IRLB protein which is thought to be important in binding to a c-myc promoter element and thus regulating its transcription (See Genbank Accession No. gi|33969). The gene encoding the disclosed cDNA is thought to reside on chromosome 1.

15 Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: WNLLWYFQRLRLPSILPGLVLASCDGPSXSQAPSPWLTPDPASVQVRLLDV  
20 LTPDPN (SEQ ID NO:978), QRGYREILFLTMAALGKDHVDIVAFDKKYKSAF  
NKLASSMGKEELRHRAQMP (SEQ ID NO:979), and/or WNLLWYFQRLRLP  
SILPGLVLAS (SEQ ID NO:980). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
25 and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

30

This gene is expressed primarily in brain and breast, and to a lesser extent in a variety of hematopoietic tissues and cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer of the brain and breast; lymphoproliferative disorders; neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, breast, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, breast, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates that the protein product of this gene is useful for the treatment and diagnosis of cancer of the brain, breast, and hematopoietic system. In addition, it is useful for the treatment of neurodegenerative disorders, as well as disorders of the hematopoietic system, including defects in immune competency and inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:131 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1936 of SEQ ID NO:131, b is an integer of 15 to 1950, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 122**

5 The translation product of this gene shares sequence homology with an ATP synthase, a key component of the proton channel that is thought to be important in the translocation of protons across the membrane.

This gene is expressed primarily in T-cell lymphoma.

10 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or  
15 lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the  
20 disorder.

The tissue distribution in T-cell lymphoma, combined with the homology to an ATP synthase indicates that the protein product of this gene is useful for the treatment of defects in proton transport, homeostasis, and metabolism, as well as the diagnosis and treatment of lymphoma. Because the gene is expressed in cells of  
25 lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:132 and may have been publicly available prior to conception



of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 976 of SEQ ID NO:132, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 123

The gene encoding the disclosed cDNA is thought to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

15 This gene is expressed primarily in a variety of fetal tissues, including fetal liver, lung, and spleen, and to a lesser extent in a variety of blood cells, including eosinophils and T cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer (abnormal cell proliferation); T cell lymphomas; and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the  
20 fetus and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. fetal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
25 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.  
30

The tissue distribution in fetal tissues indicates that the protein product of this gene is useful for the treatment and diagnosis of conditions involving cell proliferation. Similarly, the fetal tissue expression, as well as the expression in a variety of blood cell lineages, indicates that it may play a role in either cellular proliferation, apoptosis, or cell survival. Thus it may be useful in the management and treatment of a variety of cancers and malignancies. In addition, its expression in blood cells indicates that it may play additional roles in hematopoietic disorders and conditions, and could be useful in treating diseases involving autoimmunity, immune modulation, immune surveillance, and inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:133 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1706 of SEQ ID NO:133, b is an integer of 15 to 1720, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 124**

This gene is expressed primarily in placenta, and to a lesser extent in pineal gland and rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, endocrine, and female reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the placenta and endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 372 as residues: Leu-69 to Val-76.

The tissue distribution in placenta indicates that the protein product of this gene is useful for the diagnosis and treatment of developmental disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:134 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 691 of SEQ ID NO:134, b is an integer of 15 to 705, where both a and b correspond to the positions of nucleotide  
5 residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 125

10 Contact of cells with supernatant expressing the product of this gene increases the permeability of THP-1 Monocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the Monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to,  
15 activating monocyte cells.

This gene is expressed primarily in benign prostatic hyperplasia.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of benign prostatic hyperplasia. Similarly, polypeptides and  
20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, cancerous and wounded  
25 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in benign prostatic hyperplasia tissue indicates that the  
30 protein product of this gene is useful for the treatment and diagnosis of proliferative disorders of the prostate. Furthermore, the biological activity data indicates that the translation product of this gene is useful for the stimulation of certain immune system

cells, such as monocytes, which may be useful for helping the body to defend against infection. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:135 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 309 of SEQ ID NO:135, b is an integer of 15 to 323, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 126**

This gene is expressed primarily in Raji cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and T cell autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
25 disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in Raji cells indicates that the protein product of this gene is useful for treatment and diagnosis of inflammation and T cell autoimmune disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:136 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 568 of SEQ ID NO:136, b is an integer of 15 to 582, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 127**

This gene is expressed primarily in apoptotic T-cells, and to a lesser extent in suppressor T cells and ulcerative colitis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases involving premature apoptosis, and immunological and gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or

lower levels may be routinely detected in certain tissues or cell types (e.g. immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 375 as residues: Asp-23 to Gly-29.

The tissue distribution in apoptotic T-cells indicates that the protein product of this gene is useful for the treatment and diagnosis of disorders involving inappropriate levels of apoptosis, especially in immune cell lineages. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia. Furthermore, expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:137 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1007 of SEQ ID NO:137, b is an integer of 15 to 1021, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 128

The translation product of this gene shares sequence homology with an *C. elegans* coding region C47D12.2 of unknown function (See Genbank Accession No. gnl|PID|e348986).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

5 EDDGFNRSIHEVILKNITWYSERVLTEISLGSLILVVIRTIQYNMTRTRDKYLH  
 TNCLAALANMSAQFRSLHQYAAQRIISLFSLLSKKHNVLEQATQSLRGSLS  
 NDVPLPDYAQDLNVIEEVIRMMLEIINSCLTNSLHHNPNLVYALLYKRDLFEQ  
 FRTHPSFQDIMQNIDLVISFFSSRLLQAGS (SEQ ID NO:981),  
 10 EDDGFNRSIHEVILKNITWYSERVLTEISLGSLILVV (SEQ ID NO:982),  
 RTIQYNMTRTRDKYLHTNCLAALANMSAQFRSLHQYAAQRIISLFSLLSKKH  
 N (SEQ ID NO:983),  
 SCLTNSLHHNPNLVYALLYKRDLFEQFRTHPSFQDIMQNIDLVISFFSSRLLQA  
 GS (SEQ ID NO:984), KKHNVLEQATQSLRGSLSNDVPLPDYAQD (SEQ ID  
 15 NO:985), TISNSSFISGYNAKY (SEQ ID NO:986), and/or  
 LKVAASWELSCQWNGSWKSLSKASLRC PKTD (SEQ ID NO:987). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 20 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome  
 25 18. Accordingly, polynucleotides related to this invention are useful as a marker in  
 linkage analysis for chromosome 18.

This gene is expressed primarily in smooth muscle, and to a lesser extent in  
 fetal liver/spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 30 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 atherosclerosis and other cardiovascular and hepatic disorders. Similarly,



polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g. muscle, fetal liver/spleen, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the

10 disorder.

The tissue distribution in smooth muscle indicates that the protein product of this gene is useful for the diagnosis and treatment of circulatory system disorders such as atherosclerosis, hypertension, stroke, aneurysms, embolisms, and thrombosis. In addition, the tissue distribution indicates that the protein product of this gene is useful

15 for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus indicates a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue

20 trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:138 and may have been publicly available prior to conception

25 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1763 of SEQ ID NO:138, b is an

30 integer of 15 to 1777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 129**

- The translation product of this gene shares sequence homology with a
- 5 ribosomal protein which is thought to be important in cellular metabolism, in addition to the *C.elegans* protein F40F11.1 which does not have a known function at the current time (See Genbank Accession No. gnl|PID|e244552 ).
- In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- 10 MADIQTERAYQKQPTIFQNKKRVLGETGKEKLPRVTNKNIGLGFKDTPRRL  
LRGTYIDKKCPFTGNVSIRGRILSGVVTQDEDAEDHCHPPRLSALHPQVQPLR  
EAPQEHVCTPVPLLQGRPDR (SEQ ID NO:988),  
MKMQRTTIVIRRDYLHYIRKYNRFEKRRHKNMSVHLSPCFRDVQIGDIVTVGEC  
RPLSKTVRFNVLKVTKAAGTKKQFQKF (SEQ ID NO:989),
- 15 MADIQTERAYQKQPTIFQNKKRVLGETGK (SEQ ID NO:990),  
KLPRVTNKNIGLGFKDTPRRLLRGTYIDKKCPFTGNVSIRGRILSGVVTQDED  
AEDHC (SEQ ID NO:991),  
HCHPPRLSALHPQVQPLREAPQEHVCTPVPLLQGRPDR (SEQ ID NO:992),  
MKMQRTTIVIRRDYLHYIRKYNRFEKRRHKNMSVHLSP (SEQ ID NO:993),
- 20 CFRDVQIGDIVTVGECRPLSKTVRFNVLKVTKAAGTKKQFQKF (SEQ ID  
NO:994), PRLLRGTYIDKKCPFTGNVSIRGRILSGVVTQ (SEQ ID NO:995),  
SRGTGVQTCSCGASRSGCTCGCSADSLGG (SEQ ID NO:996), and/or  
QWSSASSSWVTTPERIRPRMDTLPVKGHFLSM (SEQ ID NO:997). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as
- 25 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding
- 30 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

5 This gene is expressed primarily in Wilm's tumor, and to a lesser extent in thymus and stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Kidney disorders and cancer, diseases affecting RNA translation. Similarly, 10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Wilm's tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, thymus, cancerous and 15 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID 20 NO: 377 as residues: Arg-15 to Gly-22.

The tissue distribution in Wilm's tumor, combined with the homology to a ribosomal protein indicates that the protein product of this gene is useful for diseases affecting RNA translation, in addition to proliferative disorders. Furthermore, given the tissue distribution, the translation product of this gene may be useful in treating 25 and/or detecting Wilm's tumor or tumors of other tissues mentioned previously. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are 30 related to SEQ ID NO:139 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 629 of SEQ ID NO:139, b is an integer of 15 to 643, where both a and b correspond to the positions of nucleotide  
 5 residues shown in SEQ ID NO:139, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 130

10       The translation product of this gene shares sequence homology with a yeast DNA helicase, which is thought to be important in global transcriptional regulation (See Genbank Accession No. gnl|PID|e243594).  
 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 15 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTVYRLICKGTIEERILQRAKEKSEI  
 QRMVISG (SEQ ID NO:998),  
 TRMIDLLEEYMVYRKHTYXRLDGSSKISERRDMVADFQNRNDIFVLLSTRA  
 GGLGINLTAXDTVHF (SEQ ID NO:999),  
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTVYR (SEQ ID NO:1000),  
 20 VYRLICKGTIEERILQRAKEKSEIQRMVISG (SEQ ID NO:1001),  
 TRMIDLLEEYMVYRKHTYXRLDGSSKISERRDM (SEQ ID NO:1002),  
 RRDMVADFQNRNDIFVLLSTRAGGLGINLTAXDTVHF (SEQ ID NO:1003),  
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTVYRLICKG (SEQ ID NO:1004),  
 IFYDSDWNPTVDQQAMDRAHRLGQTKQVTVYRLICKG (SEQ ID NO:1005),  
 25 RLICKGTIEERILQRAKEKSEIQRMVISG (SEQ ID NO:1006), and/or  
 GTRMIDLLEEYMVYRKHTYXRLDGSSKISERRDMVADFQNRNDIFVLLSTR  
 AGGLGINLTAXDTVHFL (SEQ ID NO:1007). Moreover, fragments and variants  
 of these polypeptides (such as, for example, fragments as described herein,  
 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
 30 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
 under stringent conditions, to the polynucleotide encoding these polypeptides ) are  
 encompassed by the invention. Antibodies that bind polypeptides of the invention are

also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in amygdala.

Polynucleotides and polypeptides of the invention are useful as reagents for  
5 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
diseases and disorders of the brain and the endocrine system. Similarly, polypeptides  
and antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of  
10 disorders of the above tissues or cells, particularly of the central nervous system,  
endocrine system, expression of this gene at significantly higher or lower levels may  
be routinely detected in certain tissues or cell types (e.g. brain, endocrine, cancerous  
and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial  
fluid and spinal fluid) or another tissue or cell sample taken from an individual having  
15 such a disorder, relative to the standard gene expression level, i.e., the expression  
level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 378 as residues: Lys-24 to Tyr-34.

The tissue distribution in amygdala, combined with the homology to a DNA  
20 helicase indicates that the protein product of this gene is useful for diseases affecting  
RNA transcription, particularly developmental disorders and healing wounds, since  
the later are thought to approximate developmental transcriptional regulation. The  
amygdala processes sensory information and relays this to other areas of the brain  
including the endocrine and autonomic domains of the hypothalamus and the brain  
25 stem. Therefore, the translation product of this gene is also useful for the detection  
and/or treatment of disorders of the endocrine and/or neural systems. Protein, as well  
as, antibodies directed against the protein may show utility as a tissue-specific marker  
and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are  
related to SEQ ID NO:140 and may have been publicly available prior to conception  
of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1206 of SEQ ID NO:140, b is an integer of 15 to 1220, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 131

10

This gene is expressed primarily in prostate, and to a lesser extent in amygdala and pancreatic tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate enlargement and gastrointestinal disorders, particularly of the pancreas and gall bladder. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in prostate indicates that the protein product of this gene is useful for the treatment and diagnosis of prostate or reproductive diseases, including benign prostatic hyperplasia and prostate cancer. In addition, the tissue distribution in tumors of the pancreas indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tissues where expression has been indicated. Protein, as well as, antibodies directed against

the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:141 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:141, b is an integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to a + 14.

## 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 132**

The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

20 This gene is expressed primarily in adult lung, and to a lesser extent in the hypothalamus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary diseases and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adult lung indicates that the protein product of this gene is useful for the diagnosis and treatment of pulmonary and respiratory disorders such as emphysema, pneumonia, and pulmonary edema and emboli. In addition, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:142 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1454 of SEQ ID NO:142, b is an integer of 15 to 1468, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 133**

This gene is expressed primarily in human liver.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,



cirrhosis of the liver and other hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human liver indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:143 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 286 of SEQ ID NO:143, b is an integer of 15 to 300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 134**

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

5 This gene is expressed primarily in fetal kidney, and to a lesser extent in fetal liver and spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, development and regeneration of liver and kidney and immunological disorders.

10 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and excretory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney,

15 liver, spleen, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 382 as residues: Pro-70 to Arg-77, Tyr-102 to Thr-107.

The tissue distribution in fetal kidney indicates that the protein product of this gene is useful for the diagnosis and treatment of diseases of the kidney and liver, such as cirrhosis, kidney failure, kidney stones, and liver failure, hepatoblastoma, jaundice,

25 hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility

30 as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:144 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2229 of SEQ ID NO:144, b is an integer of 15 to 2243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 135**

This gene is expressed primarily in brain, bone marrow, and to a lesser extent in placenta, T cell, testis and neutrophils.

15 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative and immunological diseases and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
20 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine,  
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
30 NO: 383 as residues: Met-1 to His-6.

The tissue distribution in brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral

disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in T cells and neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:145 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1068 of SEQ ID NO:145, b is an integer of 15 to 1082, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 136

25

The translation product of this gene is homologous to the human WD repeat protein HAN11, which is thought to function in signal transduction pathways. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFRLLALGSFVEEYNNKVQLV  
GLDEESSEFICRNTFDHPYPTTKLMWPDTKGVYPDLLATSGDYLRVWRVGE  
TETRLLECLLNNKNSDFCAPLTSFDWNEVDPYLLGTSSIDTTCTIWGLETGQV

30

LGRVNLVSGHVKTQLIAHDKEVYDIAFSRAGGGRDMFASVGADGSVRMFDL  
 RHLEHSTIYEDPQHHP LLRLCWNKQDPNYLATMAMDGMEVVILDVRVPAH  
 LXPGTTIEHVSMALLGPHIHPATSALQRM TTRLSSGTSSKCPEPLRTL SWPTQL  
 XGEINNVQWASTQPELSPSATT TAWRYSECSVGGAVPTRQGLLYFLPLPHPQS  
 5 (SEQ ID NO:1008),  
 MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFRLLALGSFVEEYNNKVQLV  
 GLDEESSEFICRNTFDHPYPTTKLMWIPDTKGVYPDLLATSGDYLRVVRVGE  
 TETRLECLLNNKNNSDFCAPLTSFDWNEVDPYLL (SEQ ID NO:1009),  
 SFDWNEVDPYLLGTSSIDTTCTIWGLETGQVLGRVNLVSGHVKTQLIAHDKE  
 10 VYDIAFSRAGGGRDMFASVGADGSVRMFDLRHLEHSTIYEDPQHHP LLRLC  
 WNKQDPNYLATMAMDGMEVVILDVRVPAHLXPGTTI (SEQ ID NO:1010),  
 and/or VGADGSVRMFDLRHLEHSTIYEDPQHHP LLRLCWNKQD  
 PNYLATMAMDGMEVVILDVRVPAHLXPGTTIEHVSMALLGPHIHPATSALQR  
 M TTRLSSGTSSKCPEPLRTL SWPTQLXGEINNVQWASTQPELSPSATT TAWRY  
 15 SECSVGGAVPTRQGLLYFLPLPHPQS (SEQ ID NO:1011). Moreover, fragments  
 and variants of these polypeptides (such as, for example, fragments as described  
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
 identical to these polypeptides and polypeptides encoded by the polynucleotide which  
 hybridizes, under stringent conditions, to the polynucleotide encoding these  
 20 polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome  
 17. Accordingly, polynucleotides related to this invention are useful as a marker in  
 25 linkage analysis for chromosome 17.

This gene is expressed primarily in placenta, embryo, T cell and fetal lung,  
 and to a lesser extent in endothelial, tonsil and bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 30 and for diagnosis of diseases and conditions which include, but are not limited to,  
 immunological and developmental diseases in addition to cancers. Similarly,  
 polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and  
5 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
10 NO: 384 as residues: Gly-19 to Gln-28, Pro-36 to Phe-42.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Because the gene is expressed in cells of lymphoid origin, the natural gene product  
15 may be involved in immune functions. Therefore it may also be used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:146 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4299 of SEQ ID NO:146, b is an integer of 15 to 4313, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 137

This gene is expressed primarily in TNF and INF induced epithelial cells, T cells and kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory conditions particularly inflammatory reactions in the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 385 as residues: Thr-67 to Gly-72, Gln-132 to Ala-145, Arg-150 to Pro-157.

The tissue distribution in TNF and INF induced epithelial cells indicates that the protein products of this gene are useful for treating the damage caused by inflammation of the kidney. Furthermore, the tissue distribution in kidney indicates that this gene or gene product is useful in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:147 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1169 of SEQ ID NO:147, b is an integer of 15 to 1183, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.

#### 10. **FEATURES OF PROTEIN ENCODED BY GENE NO: 138**

The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1. (See Genbank Accession No. D63485).

15 This gene is expressed primarily in breast cancer and colon cancer, and to a lesser extent in thymus and fetal spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
20 cancers, especially of the breast and colon tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
25 tissues or cell types (e.g. breast, colon, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in tumors of colon and breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as



well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:148 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:148, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 139**

The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

20 This gene is expressed primarily in CD34 positive cells, and to lesser extent in activated T-cells and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune related diseases and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 positive cells, T-cells and neutrophils indicates that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic disorders and immune related diseases, such as anemia, leukemia, inflammation, infection, allergy, immunodeficiency disorders, arthritis, asthma, immune deficiency diseases such as AIDS. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells and neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:149 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1391 of SEQ ID NO:149, b is an integer of 15 to 1405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 140**

This gene was recently published by another group, who called the gene KIAA0313 gene. (See Genbank Accession No. d1021609.)

- 5 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:
- LYATATVISSPSTEXLSQDQGDRA SLDAADSGRGSWTSCSSGSHDNIQTIQHQR  
 RSWETLPFGHTHFDYSGDPAGLWASSSHMDQIMFSDHSTKYNRQNSRESLE  
 QAQSRASWASSTGYWGEDSEGDTGTIKRRGGKDV SIEAESSSLTSVTTEETKP  
 10 VPM PAHIAVASSTTKGLIARKEGRYREPPPTPPGYIGIPITDFPEGHSH PARKPP  
 DYNVALQRSRMVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKXNESDPR  
 LAPYQSQGFSTEEDEDEQVSAV (SEQ ID NO:1012),  
 HMDQIMFSDHSTKYNRQNSRESLEQAQSRASWASSTGYWGE (SEQ ID  
 NO:1013),  
 15 SVTTEETKPVMPAHI AVASSTTKGLIARKEGRYREPPPTPPGYIGIPITD (SEQ  
 ID NO:1014), and/or  
 VALQRSRMVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKXNESDPRLAP  
 YQSQGF (SEQ ID NO:1015). Moreover, fragments and variants of these  
 polypeptides (such as, for example, fragments as described herein, polypeptides at  
 20 least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
 and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
 conditions, to the polynucleotide encoding these polypeptides ) are encompassed by  
 the invention. Antibodies that bind polypeptides of the invention are also  
 encompassed by the invention. Polynucleotides encoding these polypeptides are also  
 25 encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4. (See Genbank Accession No. AB002311 ).

- 30 This gene is expressed primarily in ovarian cancer, tumors of the Testis, brain, and colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, ovarian, testicle, brain and colon cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male and female reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, testis, colon, ovary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of colon, ovary, testis, and brain origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:150 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2876 of SEQ ID NO:150, b is an integer of 15 to 2890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.

### 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 141

The gene encoding the disclosed cDNA is thought to reside on chromosome 18. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in spleen and colon cancer.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
10 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal tract and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. spleen, colon, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid  
15 and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon tumors indicates that the protein product of this gene is useful for the diagnosis and intervention of such tumors, in addition to  
20 other tissues and cell types where expression has been indicated. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be  
25 also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and  
30 graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In

addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the  
 5 above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
 10 related to SEQ ID NO:151 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
 15 formula of a-b, where a is any integer between 1 to 2385 of SEQ ID NO:151, b is an integer of 15 to 2399, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 142

The translation product of this gene is homologous to a T cell translocation protein, a putative zinc finger factor (See Genbank Accession No. 340454), as well as to the G-protein coupled receptor TM5 consensus polypeptide (See Genbank  
 25 Accession No. R50734).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 CLLFVFSVLGMRCLFWTIVYNVLYLKHKCNVLLCYHLCSI (SEQ ID  
 NO:1016), and/or  
 30 ACSKLIPAFEMVMRAKDNVYHLDCFACQLCNQRXCVGDKFFLKNNXXLCQ  
 TDYEEGLMKEGYAPXVR (SEQ ID NO:1017). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are  
5 also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal brain, and to a lesser extent in frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, including brain cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
15 the above tissues or cells, particularly of the Central Nervous System, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's  
25 Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse  
30 formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:152 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 788 of SEQ ID NO:152, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 143

The translation product of this gene has significant homology to the Fas ligand, which is a cysteine-rich type II transmembrane protein/tumor necrosis factor receptor homolog. Mutations within this protein have been shown to result in generalized lymphoproliferative diseases leading to the development of lymphadenopathy and autoimmune disease (See Medline Article No. 94185175).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

SALSEPGAPDRRRPCPESVPRRPDDEQWPPPTALCLDVAPLPPSS (SEQ ID NO:1018). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention. (See Genbank Accession No. 473565).



This gene is expressed primarily in osteoblasts, lung, and brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoblast-related, pulmonary, neurological, and immunological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, brain, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 391 as residues: Trp-33 to Thr-40, Lys-45 to Ile-63.

The tissue distribution in osteoblasts, lung, and brain, combined with its homology to the Fas ligand, indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the Fas ligand gene is known to be expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including asthma, immune deficiency diseases such as AIDS and leukemia, and various autoimmune disorders including lupus and arthritis. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:153 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
 5 formula of a-b, where a is any integer between 1 to 447 of SEQ ID NO:153, b is an integer of 15 to 461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.

#### 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 144

This gene shares sequence homology with a 21.5 KD transmembrane protein in the SEC15-SAP4 intergenic region of yeast. (See Genbank Accession No. 1723971.)

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: PVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFI (SEQ ID NO:1019),  
 AHASESGERWWACCGVRFGLRSIEAIGRSCCHDGPGLVANRGRRFKWAIEL  
 20 SGPGGGSRRGRSDRGSGQGDSLYPVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFIMYMAGNTISIFPTMMVCMMAWRPIQALMAISATFKMLES  
 SSQKFLQGLVYLIGNLMGLALAVYKCQSMGLLPHTASDWLAFIEPPERMEFS  
 GGGLLL (SEQ ID NO:1020), PVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQIPMNLFI (SEQ ID NO:1022), and/or  
 25 ATFKMLESSQKFLQGLVYLIGNLMGLALAVYKCQSMGLLPHTASD (SEQ ID NO:1021). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 30 encoding these polypeptides ) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoclastoma, hemangiopericytoma, liver, lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoclastoma, hemangiopericytoma, liver and lung tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the above tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lung and liver systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of tumors of the osteoclastoma, hemangiopericytoma, liver and lung, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:154 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2374 of SEQ ID NO:154, b is an integer of 15 to 2388, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 145**

5 The translation product of this gene shares homology with the glucagon-69 gene which may indicate this gene plays a role in regulating metabolism. (See Genbank Accession No. A60318)

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
PTTKLDIMEKKKKHIQIRFPSFYHKLVDSGRMRSKRETRREDSDTKHNL (SEQ  
10 ID NO:1023), FLWKSLLRLRYFKMRQH (SEQ ID NO:1024), and/or  
YHYLLSSFLSYSSSSQNLVPYGRKMGTLFECVFFFP (SEQ ID NO:1025).  
Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
15 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain, kidney, colon, and testis.  
20 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain, kidney, colon, and testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
25 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, neurological, circulatory, and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, kidney, colon, testis, cancerous and wounded tissues) or bodily fluids (e.g.,  
30 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain, kidney, colon, and testis origins, indicates that the protein product of this gene is useful for the diagnosis and intervention of tumors of these tissues. The protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. The tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:155 and may have been publicly available prior to conception

of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
 5 formula of a-b, where a is any integer between 1 to 628 of SEQ ID NO:155, b is an integer of 15 to 642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 146

The translation product of this gene shares sequence homology with goliath protein, which is a Drosophila protein thought to be important in the regulation of gene expression during development. Protein may serve as a transcription factor.

15 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

TEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGSLVFVSISFI  
 VLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKGDKE  
 TDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMCKLNI

20 LKALGIV (SEQ ID NO:1026),

MTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGSLVF  
 VSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKK  
 GDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMC  
 KLNILKALGIVPNLPCTDNVAFDMERLTRTQAVNRRSALGDLAGDNSLGLPEP

25 LRTSGISPLPQDGELTPRTGEINIAVTKEWFIIASFGLLSALTLCYMIIRATASLN  
 ANEVEWF (SEQ ID NO:1027),

TEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTRMPPKNFSRGSLVFVSISFI  
 VLMISSAWLIFYF (SEQ ID NO:1028),

SISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKG

30 DKE (SEQ ID NO:1029),

VKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTC  
 PMCKLNILKALGIV (SEQ ID NO:1030),

MTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTI  
AVGTRMPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRRRL  
GDAAKKAISKLTTRT (SEQ ID NO:1031),  
AAKKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHK  
5 SCVDPWLSEHCTCPMCKLNILKALGIVPNLPC (SEQ ID NO:1032),  
TQAVNRRSALGDLAGDNSLGLEPLRTSGISPLPQDGELTPRTGEINIAVTKEWF  
IIASFGLLSALTLCYMIIRATASLNANEVEWF (SEQ ID NO:1033),  
PLHGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTFKEKISRAAFHNAVAV  
VIYNNKSKEEPVTMTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTI  
10 MPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRRRLGDAAK  
KAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCV  
DPWLSEHCTCPMCKLNILKALGIVPNLPCD NVAFDMERLTRTQAVNRRSAL  
GDLAGDNSLGLEPLRTSGISPLPQDGELTPRTGEINIAVTKEWFIIASFGLLSAL  
TLCYMIIRATASLNANEVEWF (SEQ ID NO:1034), and/or  
15 HGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTFKEKISRAAFHNAVAVVI  
YNNKSKEE (SEQ ID NO:1035). Moreover, fragments and variants of these  
polypeptides (such as, for example, fragments as described herein, polypeptides at  
least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides  
and polypeptides encoded by the polynucleotide which hybridizes, under stringent  
20 conditions, to the polynucleotide encoding these polypeptides) are encompassed by  
the invention. Antibodies that bind polypeptides of the invention are also  
encompassed by the invention. Polynucleotides encoding these polypeptides are also  
encompassed by the invention. (See Genbank Accession No. 157535).

When tested against Jurkat cell lines, supernatants removed from cells  
25 containing this gene activated the GAS assay. Thus, it is likely that this gene  
activates T-cells through the Jak-STAT signal transduction pathway. The gamma  
activating sequence (GAS) is a promoter element found upstream of many genes  
which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large,  
signal transduction pathway involved in the differentiation and proliferation of cells.  
30 Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS  
element, can be used to indicate proteins involved in the proliferation and  
differentiation of cells.

This gene is expressed primarily in macrophage, breast, kidney and to a lesser extent in synovium, hypothalamus and rhabdomyosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, schizophrenia and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and neural system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, kidney, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in macrophage, hypothalamus, and kidney, combined with the homology to a zinc finger protein indicates that the protein product of this gene is useful for the treatment of schizophrenia, kidney disease and other cancers. Furthermore, the tissue distribution in macrophage, breast, and kidney origins indicates that the protein product of this gene is useful for the diagnosis and intervention of tumors within these tissues, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:156 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is



cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:156, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide  
5 residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 147

10 The translation product of this gene shares sequence homology with HNP36 protein, an equilibrative nucleoside transporter, which is thought to be important in gene transcription as well as serving as an important component of the nucleoside transport apparatus (See Genbank Accession No. 1845345).

In specific embodiments, polypeptides of the invention comprise, or  
15 alternatively consists of, an amino acid sequence selected from the group:

MSGQGLAGFFASVAMICAIASGSELSAFIGYFITACAVIILTIICYLGLP  
RLEFYRYYYQQLKLEGPGEQETKLDLISKGEEPRAGKEESGVSVSNSQPTNESH  
SIKAILKNISVLAFSVCFTITIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLTF  
NIFDWLGRSLTAVFMWPGKDSRWLPSWXLARLVFVPLLLLCNIKPRRYLTVV  
20 FEHDAWFIFFMAAFASNGYLASLCMCFGPKKVKPAAEAETAEPSPWSSCVW  
VWHWGLFSPSCSGQLCDKGWTEGLPASLPVCLLPLPSARGDPEWSGGFFF(SE  
Q ID NO:1036),

MSGQGLAGFFASVAMICAIASGSELSAFIGYFITACAVIILTIICYLGLPRLEF  
YRYYYQQLKLEGPGEQETKLDLISKGEEPRAGKEESGVSVSNSQPTNESH  
25 (SEQ ID NO:1037),

SGVSVSNSQPTNESHSIKAILKNISVLAFSVCFTITIGMFPAVTVEVKSSIAGS  
STWERYFIPVSCFLTFNIFDWLGRS (SEQ ID NO:1038),

TIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLTFNIFDWLGRSLTAVFMWPG  
KDSRWLPSWXLARLVFVPLLLLCNIKPRRYLTVVFEHDA (SEQ ID NO:1039),

30 and/or

FGPKKVKPAAEAETAEPSPWSSCVWVWHWGLFSPSCSGQLCDKGWTEGLPAS  
LPVCLLPLPSARGDPEWSGGFFF (SEQ ID NO:1040). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments. The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in eosinophils and aortic endothelium, and to a lesser extent in umbilical vein endothelial cell and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hemopoietic disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. circulatory, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution eosinophils and aortic endothelium, combined with the homology to the HNP36 protein indicates that the protein product of this gene is useful for the treatment of blood neoplasias and other hemopoietic disease. Furthermore, elevated expression of this gene product by endothelial cells indicates that it may play vital roles in the regulation of endothelial cell function; secretion; proliferation; or angiogenesis. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:157 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:157, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.

#### 15    **FEATURES OF PROTEIN ENCODED BY GENE NO: 148**

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

20        This gene is expressed primarily in breast cancer cell lines, thymus stromal cells, and ovary.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and female reproductive system diseases including breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. thymus, ovary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having

such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast cancer cells and ovary indicates that the protein product of this gene is useful for the diagnosis and treatment of endocrine disorders. In addition, the tissue distribution in tumors of thymus, ovary, and breast origins indicates that the protein product of this gene is useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:158 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1611 of SEQ ID NO:158, b is an integer of 15 to 1625, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 149

The translation product of this gene has homology to pmt1 and pmt 2, two conserved Schizosaccharomyces pombe genes.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: DDDGFEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTFNEDE  
GELPEWVFVQEEKQHRIRQLPVGKKEVEHYRKRWREINARPIXXXXXXXXXXXX  
XXXXXXXXLEQTRKKAEAVVNTVDIXRTRES (SEQ ID NO:1041), DDDG  
FEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTF (SEQ ID

NO:1042), and/or

KRWREINARPIXXXXXXXXXXXXXXXXXXXXLEQTRKKAEAVVNTVDIXRTRES

(SEQ ID NO:1043). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
 5 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the  
 10 invention. (See Genbank Accession No. e1216734).

This gene is expressed primarily in retina and ovary, and to a lesser extent in breast cancer cells, epididymus and osteosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
 15 and for diagnosis of diseases and conditions which include, but are not limited to, neuronal growth disorders, cancer and reproductive system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and  
 20 reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. retina, ovary, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression  
 25 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 397 as residues: Met-1 to Gly-7.

The tissue distribution in ovary, breast cancer cells, and epididymus indicates  
 30 that the protein product of this gene is useful for the diagnosis or treatment of reproductive system diseases and cancers, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the

protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:159 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1673 of SEQ ID NO:159, b is an integer of 15 to 1687, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 150

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKEKKRNKKKKKTIGSPKRIQS  
 20 PLNNKLLNSPAKTLPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSGVPGLS  
 SLQSDPAGCVRPPAPNLAGAVEFNDVKTLLEWTTISDPMEEDILQVVKYCT  
 DLIEEKDLEKLDLVIKYMKRLMQQSVESVWNMAFDNFILDNVQVVLQQTYGS  
 TLKVT (SEQ ID NO:1044),  
 MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKEKKRNKKKKKTIGSPKRIQ  
 25 (SEQ ID NO:1045),  
 KRIQSPLNNKLLNSPAKTLPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSG  
 VPGLSLQSDPAGCVRPPAPNLAGAVEFNDVKTLLEWTTISDPM (SEQ ID  
 NO:1046),  
 TISDPMEEDILQVVKYCTDLIEEKDLEKLDLVIKYMKRLMQQSVESVWNMAF  
 30 DFILDNVQVVLQQTYGSTLKVT (SEQ ID NO:1047),  
 VCCKTTWTLSRIKSNAIFQTDSTDCISLFMYFITRSSFSKSFSSIRSVQYFTTW  
 RMSSSIGSEIVVIHSLSKVFTSLNSTAPARLGAGGLTQPAGSDCKLERPGTPEV

EAESSSRGFSAGGPSCFRNPSINFWGLPQAPGRVFAGLLSSLLFKGL (SEQ ID NO:1048), WTLSRIKSNAIFQTDSTDCCISLFM (SEQ ID NO:1049), FTTWRMSSSIGSEIVVIHSLSKVFTSLNSTAPARLGA (SEQ ID NO:1050), and/or GGPSCFRNPSINFWGLPQAPGRVFAGLL (SEQ ID NO:1051). Moreover,

5 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
10 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

15 This gene is expressed primarily in 12 week embryo, and to a lesser extent, in hemangiopericytoma and frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
20 developmental or neural disorders, particularly hemangiopericytoma, and other proliferative conditions, including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural system and developing systems,  
25 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 398 as residues: Leu-4 to Lys-11.

The tissue distribution in embryonic and neural tissues indicates that the protein product of this gene is useful for the treatment of growth disorders, hemangiopericytoma and other soft tissue tumors. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:160 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1828 of SEQ ID NO:160, b is an integer of 15 to 1842, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 151**

The translation product of this gene has been found to have homology to a  
5 human DNA mismatch repair protein PMS3 (See Genbank Accession No. R95250).

In specific embodiments, polypeptides of the invention comprise, or  
alternatively consists of, an amino acid sequence selected from the group:  
FCHDCKFPEASPAMNCEP (SEQ ID NO:1052), FCHDCKFPEASPAMNCEP  
(SEQ ID NO:1053), and/or HEPYAVLVI (SEQ ID NO:1054). Moreover, fragments  
10 and variants of these polypeptides (such as, for example, fragments as described  
herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
identical to these polypeptides and polypeptides encoded by the polynucleotide which  
hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
15 of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
20 and for diagnosis of diseases and conditions which include, but are not limited to,  
immune or hematopoietic disorders, such as lymphoma, immunodeficiency diseases,  
and cancers resulting from genetic instability. Similarly, polypeptides and antibodies  
directed to these polypeptides are useful in providing immunological probes for  
differential identification of the tissue(s) or cell type(s). For a number of disorders of  
25 the above tissues or cells, particularly of the immune system, expression of this gene  
at significantly higher or lower levels may be routinely detected in certain tissues or  
cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or  
bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
another tissue or cell sample taken from an individual having such a disorder, relative  
30 to the standard gene expression level, i.e., the expression level in healthy tissue or  
bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 399 as residues: Met-1 to Lys-6.

The tissue distribution in neutrophils, combined with the sequence homology to a human mismatch DNA repair enzyme indicates that the protein product of this gene is useful for diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, its homology to a known DNA repair protein would suggest the gene may be useful in establishing cancer predisposition and prevention or be of use in gene therapy applications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:161 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:161, b is an integer of 15 to 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 152

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
PQPSNFPTTVRNLPYSGAGAQPPPSNC (SEQ ID NO:1055). Moreover, fragments

and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are  
5 encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as infectious diseases and lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
20 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment of inflammation and infectious diseases. Expression  
25 of this gene product in neutrophils indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the  
30 gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such

as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:162 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:162, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 153

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA  
HSLPLHPLSASCSAPACHASDTHLLYPSTRALCPSIFAWLVAPHSVFRTNAPGP  
TPSSQSSPVFPVFPVSFMAIVCXLVCC (SEQ ID NO:1056),  
MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA  
HSLPLHPLSASCSAPACHA (SEQ ID NO:1057),

FAWL VAPHSVFRTNAPGPTPSSQSSPVFPVFPVSFMA LIVCXLVCC (SEQ ID NO:1058),

MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSA  
HSLPLHPLSASC SAPACHASDTHLLYPSTRALCPSIFAWLVAPHSVFRTNAPGP

- 5 TPSSQSSPVFPVFPVVSFMA LIVCXLVCC (SEQ ID NO:1059),  
LVNWILKLHCLNLFSGFPLYLEKNATSSAGTHPLTAFPSTLSLPHALPLPAMPP  
ILTFCTPAPVPSAPRSLPGWLLLTQCSGQMLLALPHLASLARSSLSSLFHSWLL  
LFVXLCAVDF (SEQ ID NO:1060), NLFSGFPLYLEKNATSSAGTHPL (SEQ ID  
NO:1061), and/or PHLASLARSSLSSLFHSWLL (SEQ ID NO:1062). Moreover,  
10 fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
15 of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

- Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
20 and for diagnosis of diseases and conditions which include, but are not limited to,  
immune or hematopoietic disorders, such as inflammation and infectious diseases.  
Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
25 immune system, expression of this gene at significantly higher or lower levels may be  
routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
30 the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 401 as residues: Ser-11 to Pro-17.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the treatment of infectious diseases and inflammation. Moreover, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:163 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 739 of SEQ ID NO:163, b is an

integer of 15 to 753, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 154

This gene is primarily expressed in ovary, uterus, adipose tissue, brain, and the liver.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, neural, hepatic, and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
15 disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., ovary, uterus, adipose tissue, brain, liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
20 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 402 as residues: Asn-56 to Gly-67.

25 The tissue distribution of this gene product in ovary and uterus indicates that the protein product of this gene is useful for diagnostic or therapeutic uses in the treatment of the female reproductive system, obesity, and liver disorders, particularly cancer in the above tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed  
30 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:164 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1879 of SEQ ID NO:164, b is an integer of 15 to 1893, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 155**

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in  
15 linkage analysis for chromosome 3.

This gene is expressed in multiple tissues including brain, aortic endothelial cells, smooth muscle, pituitary, testis, melanocytes, spleen, neutrophils, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
20 and for diagnosis of diseases and conditions which include, but are not limited to, immunological or vascular disorders, including immunodeficiencies, cancers of the brain and the female reproductive system, as well as cardiovascular disorders, such as atherosclerosis and stroke. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
25 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, vascular, endothelial, neural, hematopoietic, reproductive, integumentary, placental, endocrine, and cancerous and wounded  
30 tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having



such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neural tissue indicates that the protein product of this gene is useful in the treatment/detection of disorders in the nervous system, including  
5 schizophrenia, neurodegeneration, neoplasia, brain cancer as well as vascular and female reproductive disorders, including cancer within the above tissues. Moreover, the protein product of this gene may also be useful in the treatment and/or detection of other vascular disorders which include, but are not limited to, aneurysms, emboli, thrombosis, atherosclerosis, microvascular disease, or stroke. Protein, as well as,  
10 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:165 and may have been publicly available prior to conception  
15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2139 of SEQ ID NO:165, b is an  
20 integer of 15 to 2153, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 156**

25

The translation product of this gene shares sequence homology with the human gene encoding cytochrome b561 (See Genbank Accession No. P10897). Cytochrome b561 is a transmembrane electron transport protein that is specific to a subset of secretory vesicles containing catecholamines and amidated peptides. This  
30 protein is thought to supply reducing equivalents to the intravesicular enzymes dopamine-beta-hydroxylase and alpha-peptide amidase.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MAMEGYWRFLALLGSALLVGFLSVIFALVWVLHYREGLGWDGSALEFNWH  
PVLMTGTFVFIQGIIVYRLPWTWKCSKLLMKSIHAGLNAVAAILAISVVAV  
5 FENHNVNNIANMYSLHSWVGLIAVICYLLQLLSGFSVFLLPWAPLSLRAFLMP  
IHVYSGIVIFGTVIATALMGLTEKLIFSLRDPAYSTFPPEGV FVNTLGLLLVFG  
ALIFWIVTRPQWKRPKEPNSTILHPNGGTEQGARGSM PAYSGNNMDKSDSEL  
NSEVAARKRN LALDEAGQRSTM (SEQ ID NO:1063),

AHASAHASGGA EYGAL (SEQ ID NO:1064),

10 QYSQYVQSAQLGWTD SCHMLFVTASFRFFSLSASMGS AFSPSISHAHTCLFW  
NCHLWNSDCNSTYGIDRETDFFPERSCIQYIPARRCFRKYAWPSDPGVRGPHF  
LD SHQTAMETS (SEQ ID NO:1065), ASMGS

AFSPSISHAHTCLFWNCHLWNSDCNSTYG (SEQ ID NO:1066),

FVHVVARVGWHGTSCSLFSASIWMKNGRIWLLRTFPLRSGDY PKNEGPEHQ

15 DQKAKRIYENTFWRECTVCRISQGKNQFLCQSHKCCCNHCSKDDNSRINMY  
GHEKCSERKRSPWKQKD (SEQ ID NO:1067), and/or

ASIWMKNGRIWLLRTFPLRSGDY PKNEGPEHQ (SEQ ID NO:1068). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

20 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

25 The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in anergic T-cells.

30 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, and metabolic related diseases. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not

10 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 404 as residues: Pro-222 to Asn-231, Asn-238 to Gly-247, Ala-251 to Leu-264, Ala-280 to Thr-285.

The tissue distribution in anergic T-cells indicates that the protein product or

15 mRNA of this gene is useful for the treatment or diagnosis of immune system and metabolic diseases or conditions including Tay-Sachs disease, phenylketonuria, galactosemia, various porphyrias, and Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:166 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:166, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 157

The translation product of this gene shares sequence homology with collagen which is important in mammalian development. This gene also shows sequence homology with bcl-2 and the HNK-1 sulfotransferase of *Rattus norvegicus* which is thought be involved in carbohydrate biosynthesis. (See Genbank Accession No. P80988 and AF022729, respectively.) When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
PGRAGPSPGLSLQLPAEPGHPAGNLAPLTSRPQPLCRIPAVPG (SEQ ID NO:1069). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in HL-60 tissue culture cells, and to a lesser extent, in liver, breast, and uterus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological diseases, hereditary disorders involving the MHC class of immune molecules, as well as developmental disorders and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s).

For a number of disorders of the above tissues or cells, particularly of the immune and reproductive system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, hepatic, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 10        Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 405 as residues: Ser-39 to Gly-46, Leu-49 to Ala-62.

- 15        The tissue distribution in reproductive, and immune tissues, combined with the homology to collagen and the detected GAS biological activity indicates that the protein product of this gene is useful for diagnosis and treatment of hereditary MHC disorders and particularly autoimmune disorders including rheumatoid arthritis, lupus, scleroderma, and dermatomyositis, as well as many reproductive disorders, including cancer of the uterus, and breast tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 20        Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:167 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 868 of SEQ ID NO:167, b is an integer of 15 to 882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 158

This gene is expressed primarily in the amygdala region of the brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, a variety of brain disorders, particularly those effecting mood and personality, in addition to neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the amygdala indicates that the protein product of this gene is useful for the treatment and/or diagnosis of a variety of brain disorders, particularly bi-polar disorder, uni-polar depression, and dementia. Moreover, The tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role

in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:168 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1194 of SEQ ID NO:168, b is an integer of 15 to 1208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 159**

This gene is expressed in a variety of tissues and cell types including brain,  
20 smooth muscle, kidney, salivary gland, and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, renal, vascular, metabolic, or immune disorders, particularly cancers.

25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous, urinary, salivary, digestive, and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
30 tissues or cell types (e.g., neural, renal, vascular, metabolic, immune cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 407 as residues: Asp-43 to Asp-60.

5       The tissue distribution in brain, smooth muscle, and T-cells indicates that the protein product of this gene is useful for diagnosis of various neurological, and cardiovascular disorders, but not limited to cancer within the above tissues. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene  
10       product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15       Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:169 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
20       cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1244 of SEQ ID NO:169, b is an integer of 15 to 1258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 160**

30       The translation product of this gene shares sequence homology with collagen, which is thought to be important in cellular interactions, extracellular matrix formation, and has been found to be an identifying determinant in autoimmune disorders. Moreover, this gene shows sequence homology with the yeast protein,



- Sls1p, an endoplasmic reticulum component involved in the protein translocation process in the Yeast *Yarrowia lipolytica*. (See Genbank Accession No. 1052828; see also J. Biol. Chem. 271, 11668-11675 (1996).) In *Mus musculus*, this same region shows sequence homology with the heavy chain of kinesin. (See Genbank Accession
- 5 No. 2062607.) Recently, suppression of the heavy chain of kinesin was shown to inhibit insulin secretion from primary cultures of mouse beta-cells. (See Endocrinology 138 (5), 1979-1987 (1997).) Moreover, kinesin was found associated with drug resistance and cell immortalization. (See Genbank Accession No. 468355.) Thus, it is likely that this gene also acts as a genetic suppressor element.
- 10 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: ARGRRRGRLELWELCLPLGCRRRRSLTMAPQSLPSSRMAPLG (SEQ ID NO:1070),
- NGQASTAKMSSCLRSPPTLAPLSLTSGIPVQSWCGASSQLLQQAVDRAQQLL
- 15 EVALVLTILQLQAGQHLVLSLQAGQCPAELGVLTVAVPAGGQEDAQCLQHL
- LTGIMLGQRQEVGRDLAPALFPQAWQEVYLAILLQLLWGHLGQLSLLLGEH
- LLRDQVVEQCDHAHGEHLRALLLHQGPQDLQPPQLQELPLGIGEVAQQGAQ
- CKQDLLLCSERLLRGQDDQQLQGSPFDGLHDLGVAGKGSAQHKRSILLHE
- GLCAVQPIDHHLKTTKGKQVLRIVHLMDIIFKIKERSNLLFQTGAGTIELVDQP
- 20 YHDLHVSNDNIQLIKVFLQFLNGAEEPLYLSLPCLVFL (SEQ ID NO:1071),
- QHLVLSLQAGQCPAELGVLTVAVPAGGQEDAQC (SEQ ID NO:1072),
- QLSLLLGEHLLRDQVVEQCDHAHGEH (SEQ ID NO:1073), GS
- PFDGLHDLGVAGKGSAQHKRSILLHEGLC (SEQ ID NO:1074), and/or
- HLMDII FKIKERSNLLFQTGAGTIELVDQP (SEQ ID NO:1075). Moreover,
- 25 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides
- 30 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

5 This gene is expressed primarily in the greater omentum, and to a lesser extent in gall bladder, stromal bone marrow cells, lymph node, liver, testes, pituitary, and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the endocrine, gastrointestinal, and immunological systems, including autoimmune disorders and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, metabolic, immune, hematopoietic, hepatic, reproductive, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 408 as residues: Asn-27 to Leu-47, Gln-81 to Lys-88, Asp-93 to Lys-102, Asn-107 to Leu-116, Met-129 to Glu-141, Glu-150 to Asp-157, Lys-176 to Glu-185, Glu-25 333 to Tyr-349, Cys-393 to Leu-403, Gln-423 to Gly-429.

The tissue distribution within gastrointestinal, endocrine and immunological tissues, combined with the sequence homology to a conserved collagen motif, indicates that the protein product of this gene is useful for the diagnosis of various autoimmune disorders including, but not limited to, rheumatoid arthritis, lupus erythromatosus, scleroderma, and dermatomyositis. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders

including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:170 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:170, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 161**

This gene has homology to the tissue inhibitor of metalloproteinase 2. Such inhibitors are vital to the proper regulation of metalloproteins such as collagenases,  
20 which has implications for tissue regeneration and autoimmune disorders (See Genbank Accession No. P16368). When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells cells through the JAK-STAT signal transduction pathway. GAS is a promoter element  
25 found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In addition, this  
30 gene maps to chromosome 17, and therefore, may be used as a marker in linkage analysis for chromosome 17 (See Genbank Accession No. P16368).

This gene is expressed primarily in several types of cancers including osteoclastoma, chondrosarcoma, and rhabdomyosarcoma, and to a lesser extent, in non-malignant tissues including synovium, amygdala, testes, and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or integumentary disorders, particularly cancers of bone and cartilage, as well as various autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculoskeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, integumentary, synovium, muscle, fibroids, reproductive, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 409 as residues: Thr-24 to Thr-34.

The tissue distribution in various cancers, combined with the sequence homology to a collagenase inhibitor and the detected GAS biological activity, indicates that the protein product of this gene is useful for the detection of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. The expression of this gene product would also suggest a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, as well as, connective tissue disorders (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and

specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the  
5 above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:171 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1989 of SEQ ID NO:171, b is an integer of 15 to 2003, where both a and b correspond to the positions of nucleotide  
15 residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 162**

20 This gene is homologous to the mitochondrial ATP6 gene, and therefore is likely a homolog of this gene family (See Genbank Accession No. X76197).

This gene is expressed primarily in brain tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
25 and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, including, but not limited to, neurodegenerative conditions, Down's syndrome, depression, Schizophrenia, and epilepsy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
30 disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded

tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5           The tissue distribution in brain tissue indicates this gene is useful for diagnosis of various neurological disorders including, but not limited to, brain cancer. Additionally the gene product may be used as a target in the immunotherapy of cancer in the brain as well as for the diagnosis of metabolic disorders such as obesity, Tay-Sachs disease, phenylketonuria and Hurler's Syndrome. Similarly, the protein product
- 10 of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and
- 15 infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function.
- 20 Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies
- 25 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:172 and may have been publicly available prior to conception
- 30 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 772 of SEQ ID NO:172, b is an integer of 15 to 786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.

5

### FEATURES OF PROTEIN ENCODED BY GENE NO: 163

The translation product of this gene was found to have homology to the MRS3 and 4 protein of *Saccharomyces cerevisiae* (See Genbank Accession No. gi|3996 ), which is known to suppress a splice defect in mitochondrial by possibly serving to modulate the cation-solute concentration in mitochondria.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

15 DEPCPPPAASCAPPSWRMELRTGSVGSQAVARRMDGDSRDGGGGKDATGSE  
DYENLPTSASVSTHMTAGAMAGILEHSVMYPVDSVKTRMQSLSPDKAQYT  
SIYGALKKIMRTEASGGPCEASTS (SEQ ID NO:1076),  
RMELRTGSVGSQAVARRMDGDSRDGGGGKDATGS (SEQ ID NO:1077),  
and/or PVDSVKTRMQSLSPDKAQYTSIYGAL (SEQ ID NO:1078). Moreover,  
20 fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
25 of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

30 This gene is expressed primarily in placenta, neutrophils, and microvascular endothelial cells, and to a lesser extent, brain, prostate, spleen, thymus, and bone.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, vascular, or reproductive disorders. Similarly, polypeptides and antibodies  
5 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, vascular, endothelial, reproductive, neural,  
10 skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 164**

The gene encoding the disclosed cDNA is believed to reside on chromosome  
20 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in neutrophils, monocytes, bone marrow, and fetal liver.

Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system or hematopoietic disorders including, but not limited to, autoimmune disorders such as lupus, leukemia and immunodeficiency disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
30 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be



5 routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, hepatic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in various immune system tissues indicates that the protein product of this gene is useful for the diagnosis of various immunological disorders such as Hodgkin's lymphoma, arthritis, asthma, immune deficiency diseases  
10 such as AIDS, and leukemia. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow  
15 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of  
20 various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:174 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30 formula of a-b, where a is any integer between 1 to 1355 of SEQ ID NO:174, b is an integer of 15 to 1369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 165**

5       The translation product of this gene shares sequence homology with dystrophin which is thought to be defective in both Duchene and Becker Muscular Dystrophy.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

- 10 MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDRWELLQA  
QALSKELRMKQNLQKWQQFNSDLNSIWA WLGDTEEELEQLQRLELSTDIQTI  
ELQIKKLKELQKAVDHRKAIL SINLCSPEFTQADSKESRDLQDRLXQMNGRW  
DRVCSLLEEW RGLLQDALMQCQGFHEMSHGLLLMLENIDRRKNEIVPIDSNL  
DAEILQDHHKQLMQIKHELLESQLRVASLQDMSCQLLVNAEGTDCLEAKEK  
15 VHVIGNRLKLLLKEVSRHIKELEKLLDVSSSQDLSSWSSADELDTSGSVSPX  
SGRSTPNRQKTPRGKCSLSQPGPSVSSPHSRSTKGGSDSSLSEXPGRSGRGFL  
FRVLRAALPLQLLLLLLIGLACL VPMSEEDYSCALSNNFARSFHPMLRYTNGP  
PPL (SEQ ID NO:1079),  
MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDRWELLQA  
20 QALSKELRMKQNLQKWQQFNSDLNSIWA WLGDTEEELEQLQRLELSTDIQTI  
ELQIK (SEQ ID NO:1080),  
KLKELQKAVDHRKAIL SINLCSPEFTQADSKESRDLQDRLXQMNGRWDRVC  
SLLEEW RGLLQDALMQCQGFHEMSHGLLLMLENIDRRKNEIVPIDSNLDAEIL  
QDHHKQLMQIKHELLESQLRVASLQDMSCQL (SEQ ID NO:1081),  
25 QDMSCQLLVNAEGTDCLEAKEKVHVIGNRLKLLLKEVSRHIKELEKLLDVSS  
SQDLSSWSSADELDTSGSVSPXSGRSTPNRQKTPRGKCSLSQPGPSVSSPHS  
(SEQ ID NO:1082),  
DSSLSEXPGRSGRGFLFRVLRAALPLQLLLLLLIGLACL VPMSEEDYSCALSN  
NFARSFHPMLRYTNGPPPL (SEQ ID NO:1083),  
30 QRFLPPGSCXLIRGPQCPRVTDPTTGQSLDDSRFQIQQTENIRSKTPTGPELDT  
SYKGY (SEQ ID NO:1084),  
SISASRLESIGTISFFLLSMFSSIRSKPWLISWKPWHCIRASCSRPRHSSSREHTR

SQRPFCXKRSCRSRLSLLSAWVNSGLQRLMERMMALRWSTAFWSSLSFLIW  
SSMVWMSVLSSRRWSCSNSSSVSPSQAQMLFKSELNCCHFWRFCFILNSLLN  
AWAWRSSHRSTPAVWVSVLCRLTKPGRLLSSSSFSLCSSLFTESILLHSPSSF  
M (SEQ ID NO:1085), TAFWSSLSFLIWSSMVWMSVLSSRRWSCSNSSSVS  
5 (SEQ ID NO:1086), LLNAWAWRSSHRSTPAVWVSVLCRL (SEQ ID NO:1087),  
LARHVLQRGYSELGFQQLMLYLHKL FVMVLKYLCIKVRINRDNFIFPSVNVL  
QHKKQTMAHFMETLALHQGILQQAPLLQQRASVPAPIHLXQAILQVPALL  
AVSLGELRAAEIDGEDDGFAVVHSFLELLELFDLELDGLDVSAEFQTLELFQL  
LLRVPQPGPDAVQV (SEQ ID NO:1088),  
10 YSELGFQQLMLYLHKL FVMVLKYLCIKV (SEQ ID NO:1089),  
AMVCFLCWRTLTEGK (SEQ ID NO:1091), and/or  
VHSFLELLELFDLELDGLDVSAEFQTELEL (SEQ ID NO:1090). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
15 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

20 This gene maps to chromosome 6, and therefore, may be used as a marker in  
linkage analysis for chromosome 6 (See Genbank Accession No. N62896).

This gene is expressed in numerous tissues including the heart, kidney, and  
brain.

Polynucleotides and polypeptides of the invention are useful as reagents for  
25 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
musculoskeletal disorders including Muscular Dystrophy and cardiovascular diseases.  
Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
30 type(s). For a number of disorders of the above tissues or cells, particularly of the  
muscle tissues, expression of this gene at significantly higher or lower levels may be  
routinely detected in certain tissues or cell types (e.g., muscle, heart, and cancerous

and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5       The tissue distribution in heart, combined with the homology to the human dystrophin gene indicates that the protein product of this gene is useful for the diagnosis and treatment of Muscular Dystrophy and other muscle disorders, particularly musculodegenerative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets  
10       for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:175 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
15       excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2365 of SEQ ID NO:175, b is an integer of 15 to 2379, where both a and b correspond to the positions of nucleotide  
20       residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 166

25       In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:  
GAGVGTAMPRVPQSAGGAVTWWGVGLSQPSSVQGGARPGTVPGTGPGPLPG  
LSPAPPPQHPPPLPKLFLCLSLXSLPQDFSLLLCLSLDPCPSSTSDL (SEQ ID  
NO:1092), GTVPGTGPGLPGLSPAPPPQHPPPLPKLFL (SEQ ID NO:1093),  
30       APSRCRRSVVQVPYSAFSSCSWTPTALRRGVLLYAGLSTSSASKAQGWHLG  
LEYPGAIMEVGRGRGGDRYAQGPSKCWRGCXLVGSGSVTAILCPGWGKAW  
DSARHPRTPSRLVSCSTASTPPTPAQAVSPLPLXFPAPGLLSSPLPLLGPLPFLY

L (SEQ ID NO:1094), TALRRGVLLYAGLSTSSASKAQGWHCLGLEYPGAIM  
(SEQ ID NO:1095), AILCPGWGKAWD SARHPRTPSRLVSCSTASTPP (SEQ ID  
NO:1096),

PPVFMASHRPXGMEPGEWRFVLVHIAFXCAWDLVCEHVSVC SQVRGRGRA  
5 GVQGEAEEKREVLGQGXR EAEKQLGQGWGV LRRWSRRQAWKGSWGAW  
HCPRPCPTLDRGWL (SEQ ID NO:1097), and/or  
HVSVC SQVRGRGRAGVQGEAEEKREVLGQ (SEQ ID NO:1098). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in human cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
diseases of the central nervous system, including Alzheimer's Disease, Parkinson's  
20 Disease, ALS, and mental illnesses. Similarly, polypeptides and antibodies directed  
to these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the central nervous system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues or cell  
25 types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
taken from an individual having such a disorder, relative to the standard gene  
expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
individual not having the disorder.

30 Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 414 as residues: Pro-20 to Gly-26, Leu-37 to Pro-42, His-57 to Gly-63.

The tissue distribution in human cerebellum indicates that the protein products of this gene are useful for the treatment/diagnosis of diseases of the central nervous system and may protect or enhance survival of neuronal cells by slowing progression of neurodegenerative diseases. Moreover, the protein product of this gene is useful  
5 for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms,  
10 hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene  
15 product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against  
20 the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:176 and may have been publicly available prior to conception  
25 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30 formula of a-b, where a is any integer between 1 to 1334 of SEQ ID NO:176, b is an integer of 15 to 1348, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 167**

In specific embodiments, polypeptides of the invention comprise, or  
5 alternatively consists of, the following amino acid sequence:  
MKLLICGNYLAPSHSESSRRCCLLCFYPLCLEINFGMKVFLSMPFLVLFQSLIQ  
ED (SEQ ID NO:1099). Moreover, fragments and variants of this polypeptide (such  
as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
10 encoded by the polynucleotide which hybridize, under stringent conditions, to the  
polynucleotide encoding this polypeptide are encompassed by the invention.  
Antibodies that bind polypeptides of the invention are also encompassed by the  
invention. Polynucleotides encoding this polypeptide are also encompassed by the  
invention.

15 The gene encoding the disclosed cDNA is believed to reside on chromosome  
15. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 15.

This gene is expressed primarily in human testes tumor, and to a lesser extent,  
in normal human testes.

20 Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
diseases of the testes, particularly cancer, and other reproductive disorders. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
25 immunological probes for differential identification of the tissue(s) or cell type(s).  
For a number of disorders of the above tissues or cells, particularly of the male  
reproductive tissues, expression of this gene at significantly higher or lower levels  
may be routinely detected in certain tissues or cell types (e.g., reproductive, testicular,  
and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal  
30 fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human testicular tissue indicates that the protein products of this gene are useful for the treatment/diagnosis of reproductive diseases including cancers. Moreover, the protein may possibly have utility as a contraceptive or may be used to ameliorate disorders related to aberrant male secondary characteristics (e.g. hair, etc.). Protein, as well as, antibodies directed against the protein may, show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:177 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1488 of SEQ ID NO:177, b is an integer of 15 to 1502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 168

The translation product of this gene was found to have homology to the gar2 gene product of Schizosaccharomyces pombe, which is thought to be involved in protein metabolism (See Genbank Accession No. gi|663262).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:  
 FSSPQGLKFRSKSSLANYLHKNGETSLKPEDFTVL SKRGIKSR YKDCS (SEQ  
 ID NO:1100),  
 ELLCYICWKNTGLFSFFLSVFRGMVSSVKSFLVGEQLLSISEPRFKMSVCKCSF  
 LSTTSTFVPISSDSKKVSSYFSLCSESLAEQNLFMMPEVFCSEQKFDPELNDLSF



FFTRLFSSLVTLRVSPHAPASEMQTVLS (SEQ ID NO:1101), and/or  
TFVPISSDSKKVSSYFSLCSESLAEQNLFMMPFVFC (SEQ ID NO:1102).

Moreover, fragments and variants of these polypeptides (such as, for example,  
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
5 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
encoding these polypeptides) are encompassed by the invention. Antibodies that bind  
polypeptides of the invention are also encompassed by the invention. Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

10 The gene encoding the disclosed cDNA is believed to reside on chromosome  
3. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 3:

This gene is expressed primarily in fetal liver.

Polynucleotides and polypeptides of the invention are useful as reagents for  
15 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
hepatic disorders, in addition to conditions affecting hematopoietic development and  
metabolic diseases. Similarly, polypeptides and antibodies directed to these  
polypeptides are useful in providing immunological probes for differential  
20 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the hepatic system, and fetal hematopoietic system,  
expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues or cell types (e.g., hepatic, metabolic, hematopoietic, and  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, bile, plasma,  
25 urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
30 NO: 416 as residues: His-7 to Trp-17, Leu-19 to Lys-27, Pro-33 to Gly-44, Lys-68 to  
Gly-74, Lys-85 to Cys-95.

The tissue distribution in liver, combined with the homology to the gar2 protein, indicates that the protein products of this gene are useful for the treatment/diagnosis of diseases of the developing liver and hematopoietic system, and act as a growth differentiation factor for hematopoietic stem cells. Moreover, the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition, the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders, and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:178 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of SEQ ID NO:178, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.

## 25 . **FEATURES OF PROTEIN ENCODED BY GENE NO: 169**

The polypeptide encoded by this gene is believed to be a membrane bound receptor.

Additionally, the extracellular domain of this polypeptide is expected to comprise the following amino acid sequence:

RILLVKYSANEENKYDYLPPTVNVCSLVKLVFCVLVSFCVIKKDHQSRNLK  
YASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAVIFS NFSITTALLF

RIVLKXRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHHD AFFSPSNS  
CLLFRNECPRKDNCTAKEWTFPEAKWNTTARVFSHRLGMGHVLIIVQCFISS  
MANYNEKILKEGNQLTEXIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGF  
FYGHS (SEQ ID NO:1103), TVNVCESELVKLVFCVLVSFCVIKKDHQSRN (SEQ  
5 ID NO:1104), LIVFYVLSYLQPAMAVIFS NFSIITTALLFR (SEQ ID NO:1105),  
FFSP SNSCLLFRNECPRKDNCTAKEWT (SEQ ID NO:1106), and/or  
YFFGILFNGLTL GLQRSNRDQIKNCGFF (SEQ ID NO:1107). Accordingly,  
preferred polypeptides encoded by this gene comprise the extracellular domain, as  
shown above. It will be recognized, however, that deletions of either end of the  
10 extracellular domain up to the first cysteine from the N-terminus and the first cysteine  
of the C-terminus, is expected to retain the biological functions of the full-length  
extracellular domain, because the cysteines are thought to be responsible for  
providing secondary structure to the molecule. Thus, deletions of one or more amino  
acids from either end (or both ends) of the extracellular domain are contemplated. Of  
15 course, further deletions including the cysteines are also contemplated as useful, as  
such polypeptides is expected to have immunological properties such as the ability to  
evoke an immune response. Polynucleotides encoding all of the foregoing  
polypeptides also encompassed by the invention.

This gene is expressed primarily in human osteoclastoma, and to a lesser  
20 extent, in hippocampus and chondrosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
skeletal or connective tissue disorders, particularly cancers. Similarly, polypeptides  
25 and antibodies directed to these polypeptides are useful in providing immunological  
probes for differential identification of the tissue(s) or cell type(s). For a number of  
disorders of the above tissues or cells, particularly of the skeletal system, expression  
of this gene at significantly higher or lower levels may be routinely detected in certain  
tissues or cell types (e.g., skeletal, neural, immune, connective, and cancerous and  
30 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid  
and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 417 as residues: Met-1 to Cys-6, Ala-41 to Tyr-49, Lys-76 to Lys-84.

5       The tissue distribution in osteoclastoma and chondrosarcoma indicates that the protein products of this gene are useful for the diagnosis of cancers of the bone and connective tissues, and may act as growth factors for cells involved in bone or connective tissue growth. Moreover, this gene product may show utility in the detection and treatment of disorders and conditions affecting the skeletal system, in  
10       particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis, as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e.  
15       spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
20       available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:179 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
25       more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2897 of SEQ ID NO:179, b is an integer of 15 to 2911, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 170**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
NSVPNLQTLAVLTEAIGPEPAIPRXPREPPVATSTPATPSAGPQPLPTGTVLVPG  
GPAPPCLGEAWALLLPPCRPSLTSCFWSPRPSWKETGV (SEQ ID NO:1108),  
5 VTAGRVGGGGPMPPQGKVGQDPQGPARSRLGGAGARQRVWQVWTWQ  
QAAPGGXGGWRALGQWPQ (SEQ ID NO:1109),  
STPATPSAGPQPLPTGTVLVPGGPAP (SEQ ID NO:1110), and/or  
QDPQGPARSRLGGAGARQR (SEQ ID NO:1111). Moreover, fragments and  
variants of these polypeptides (such as, for example, fragments as described herein,  
10 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
under stringent conditions, to the polynucleotide encoding these polypeptides) are  
encompassed by the invention. Antibodies that bind polypeptides of the invention are  
also encompassed by the invention. Polynucleotides encoding these polypeptides are  
15 also encompassed by the invention.

This gene is expressed primarily in hematopoietic progenitor cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
20 hematopoietic or immune disorders, particularly cancer and autoimmune disorders.  
Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
blood/circulatory system, expression of this gene at significantly higher or lower  
25 levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic,  
immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
from an individual having such a disorder, relative to the standard gene expression  
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
30 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 418 as residues: Gln-4 to His-10, Pro-25 to His-32.

The tissue distribution in hematopoietic progenitor cells indicates that the protein products of this gene are useful for diagnosis of diseases involving growth differentiation of hematopoietic cells. Moreover, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:180 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:180, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 171

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
ALQLAFYPDAVEEWLEENVHPSLQRLQXLLQDLSEVSAPP (SEQ ID

- NO:1112), CHPPALAGTLLRTPEGRAHARGLLLEAGGA (SEQ ID NO:1113),  
 GSSSTRSWFSTSSPQRSASWHSGAPSCRSWRLPCSWLSTRMPWRSWGRKTCT  
 PACSGCK (SEQ ID NO: 1114),  
 ASTLQPSLSPSSPPLXPPVETAVXSRALRREGAGSFPGSNILALVTQVSLHLRSS  
 5 VDALLEGNRYVTGWFSPLYHRQRKLHPV (SEQ ID NO:1115),  
 PLGPEKAGLAXPLVXHAARPCPSTSLQSQCSPLXXEPXXPPRSXVISGGFDE  
 DVKAKVENLLGISSLEKTDVPRQAPCSPPCPLLPLPFXRPWRQLFSAGLSAGR  
 GPAPSLAATSLPLSHKSASICAALWMRCWRATGMSLAGSAPTTASGSSSTRS  
 WFTSSPQRSASWHSGAPSCRSWRLPCSWLSTRMPWRSWGRKTCTPACSGC  
 10 KLCRTSARCLPPRCHPPALAGTLLRTPEGRAHARGLLLEAGGALXXXAW  
 AIRPTWASCPAQCLAHTQFLRALGSPWGRD (SEQ ID NO:1116),  
 FQEDLMKMLKRKWRTFSGFPAWKKRTLLGKHPAALVPFFPSPSPARGDSCX  
 QQGSPQGGGRLLPWQQHPCPCHTSQPPSAQLCGCAAGGQQVCHWLQPLPP  
 PAEAHPPGHGSAHPARSAQPPGTVEHPRAGAGGCPAAGFLPGCRGGVAGGK  
 15 RAPQPAAAAXSAAGPQRGVCPAATHQPWQGRCSGPLRGELMPGGSCWRL  
 GGLCXXXWPGQYGPRGRRALWPSSVLPTLSS (SEQ ID NO:1117),  
 ALPSGVLSNVPARAGGWQRGGRHLAEVLQQSLQPLQAGVHVFLQPLLHGIR  
 VESQLQGSLLQLLHEGAPLCQEAERCGLDVLNHDRVDELPLAVVGAEPASDIP  
 VALQQRIHRAAQMEADLCDKGKDVAAREGAGPLPAESPAENSCLHGRXKGR  
 20 GRRGQGGGLQGACLTGSVFSRLEIPRRFSTFALTSSSNPPEITXXRGGXGXXXXR  
 EGLHWDCLVLGHGRAAWXTNGQANPAFSGPKG (SEQ ID NO:1118),  
 RQLFSAGLSAGRGPAPSLAATSLPLSHKS (SEQ ID NO:1119),  
 ELPLAVVGAEPASDIPVALQQRIHRAAQ (SEQ ID NO:1120), and/or  
 QPPGTVEHPRAGAGGCPAAGFLPGCRG (SEQ ID NO:1121). Moreover,  
 25 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
 30 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

The protein product of this gene shares sequence homology with metallothionines. Thus, polypeptides encoded by this gene are expected to have metallothionine activity. Furthermore, such activities are known in the art and described elsewhere herein.

5        This gene is expressed primarily in kidney cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal disorders, particularly diseases of the kidney including cancer and renal  
10    dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal,  
15    urogenital, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20        Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 419 as residues: Ser-47 to Gln-52.

The tissue distribution in kidney cortex indicates that the protein product of this gene is useful for the treatment/diagnosis of diseases of the kidney, including kidney failure. Moreover, this gene or gene product could be used in the treatment  
25    and/or detection of kidney diseases including nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies  
30    directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:181 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 954 of SEQ ID NO:181, b is an integer of 15 to 968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 172**

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences: SVFERTNEFRDVLWSSI (SEQ ID NO:1122),  
 GVVQVTFMSSVSRVTWGCQPSICPGAPPAAALAGGLRLLFERELFGLPVSSPL  
 ICSFLEHHPRTSPPPSDCELLEGRSCVLLFIFLSPEPCTDPGMW (SEQ ID  
 NO:1123),  
 SKQIHSFVHSFIHLFNTHLLSTYHIPGSVQGS GDRKMNRRTQLLPSRSSQSDGG  
 GDVLGWCSKKEQIRGEETGRPNSSLSKRSLRPPARAAAGGAPGQMLG (SEQ  
 ID NO:1124), VTWGCQPSICPGAPPAAALAGGLRLLFE (SEQ ID NO:1125).  
 and/or EQIRGEETGRPNSSLSKRSLRPP (SEQ ID NO:1126). Moreover, fragments  
 and variants of these polypeptides (such as, for example, fragments as described  
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
 identical to these polypeptides and polypeptides encoded by the polynucleotide which  
 hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
 of the invention are also encompassed by the invention. Polynucleotides encoding  
 these polypeptides are also encompassed by the invention.

This gene is expressed primarily in 12 week old early stage human.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these

5 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing embryo, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, and cancerous and wounded tissues) or bodily fluids (e.g.,

10 lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID

15 NO: 420 as residues: Gln-31 to Thr-43, Gly-51 to Ser-58, Pro-65 to Pro-72.

The tissue distribution in embryonic tissue indicates that the protein product of this gene is useful for treatment/diagnosis of developmental conditions. The gene may be involved in vital organ development in the early stage, especially hematopoiesis, the cardiovascular system, and neural development. Moreover,

20 expression within embryonic tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again

25 be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

30 related to SEQ ID NO:182 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1114 of SEQ ID NO:182, b is an integer of 15 to 1128, where both a and b correspond to the positions of nucleotide  
5 residues shown in SEQ ID NO:182, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 173**

10 The translation product of this gene shares sequence homology with TGN38, an integral membrane protein previously shown to be predominantly localized to the trans-Golgi network (TGN) of cells. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

15 This gene is expressed primarily in developing embryo, and to a lesser extent, in cancer tissues including lymphoma, endometrial, prostate and colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
20 developmental abnormalities and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or  
25 cell types (e.g., developmental, reproductive, immune, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
30 individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 421 as residues: His-65 to Ser-72, Pro-82 to Gly-91, Pro-98 to Glu-118, Ser-126 to Gly-166, Pro-180 to Asp-188, Tyr-209 to Lys-214, Gln-220 to Leu-228.

The tissue distribution in the embryo, combined with the homology to an integral membrane protein indicates that the protein product of this gene is useful for the diagnosis of cancers and developmental abnormalities where aberrant expression relates to an abnormality. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:183 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2262 of SEQ ID NO:183, b is an integer of 15 to 2276, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 174**

The translation product of this gene shares sequence homology with a dnaJ heat shock protein from E. coli which is allelic to sec63, a gene that affects transit of nascent secretory proteins across the endoplasmic reticulum in yeast.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:  
 QWEHLLLLPHLLRGAHRDPGDILPLAPRSECRANSIKEYQKSIWKVYVVRRLRL  
 LKPQPNIPTVKKIVLLAGWALFLFLAYKVSKTREYQEYNPYEVLNLDPGAT  
 5 VAEIKKQYRLLSLKYHPDKGGDEV (SEQ ID NO:1127),  
 EERGGGGGAMAGQQFQYDDSGNTFFYFLTSFVGLIVIPATYYLWPRDQNAEQ  
 IRLKNIRKVYGRG (SEQ ID NO:1128),  
 RLYTGCVIFDLVSNRALSFRCLCCNSCHSASSSLFCFSSCSLSESLSPSSFSL  
 WESLLVSSSSSESLPLSETSSSSSFTAASFPTTFFACFCFCCFDCGNSTGVGFFFK  
 10 GFFFFDLAVFLGPLLFCCHPPFVLFLLVSPCPSSAGCSSAAQMDCSFSNTSAIV  
 CLVNLNTNTVTKDPTVMLLLSSSSNTCDFISMVITYGKLPRTAITSSYFSSSRKCS  
 RV (SEQ ID NO:1129), YQKSIWKVYVVRRLRLKPQPNIPTVKKIVLLAGW  
 (SEQ ID NO:1130), and/or CHPPFVLFLLVSPCPSSAGCSSAAQMDCSFSNTSA  
 (SEQ ID NO:1131). Moreover, fragments and variants of these polypeptides (such  
 15 as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%,  
 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides  
 encoded by the polynucleotide which hybridizes, under stringent conditions, to the  
 polynucleotide encoding these polypeptides) are encompassed by the invention.  
 Antibodies that bind polypeptides of the invention are also encompassed by the  
 20 invention. Polynucleotides encoding these polypeptides are also encompassed by the  
 invention.

This gene is expressed primarily in Hodgkin's lymphoma, and to a lesser extent, in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for  
 25 differential identification of the tissue(s) or cell type(s) present in a biological sample  
 and for diagnosis of diseases and conditions which include, but are not limited to,  
 immune or hematopoietic disorders, particularly cancer. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological  
 probes for differential identification of the tissue(s) or cell type(s). For a number of  
 30 disorders of the above tissues or cells, particularly of the immune system, expression  
 of this gene at significantly higher or lower levels may be routinely detected in certain  
 tissues or cell types (e.g., immune, hematopoietic, reproductive, testicular, and

cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
5 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 422 as residues: Val-37 to Pro-49, His-76 to Asp-82, Thr-97 to Trp-105, Arg-158 to Asp-165, Glu-199 to Asp-214, Asn-229 to Pro-236, Thr-261 to Gln-266, Arg-292 to Glu-298, Glu-335 to Lys-351, Glu-372 to Glu-377, Leu-398 to Asn-405, Glu-437  
10 to Pro-480, Gln-487 to Gln-495, Lys-507 to Ala-555, Ser-563 to Arg-569, Pro-588 to Glu-593, Lys-618 to Val-623, Pro-630 to Asn-635, Ser-644 to Gly-649, Lys-664 to Trp-673, Gly-679 to Phe-689, Asp-691 to Asp-704.

The tissue distribution in Hodgkin's lymphoma, combined with the homology to dnaJ and sec63 indicates that the protein product of this gene is useful as a  
15 diagnostic for cancer, that the protein may be useful in regulating gene expression levels, and that it is essential for normal protein metabolism. Therefore, protein products of this gene may show utility as an anticancer agent, or even serve to protect from viral or bacterial infections, based upon its homologous function as a protein chaperone. Protein, as well as, antibodies directed against the protein may show  
20 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:184 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3360 of SEQ ID NO:184, b is an integer of 15 to 3374, where both a and b correspond to the positions of nucleotide  
30 residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 175**

The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5. Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of chondrocytes to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both chondrocytes, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating chondrocytes.

This gene is expressed primarily in endothelial cells, and to a lesser extent, in bone marrow stromal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, endothelial, or vascular disorders, such as diseases involving angiogenic abnormalities including diabetic retinopathy, macular degeneration, and other diseases including arteriosclerosis and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, endothelial, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates that the protein products of this gene are useful for treating diseases where an increase or decrease in angiogenesis is indicated and as a factor in the wound healing process. In addition,

the protein product of this gene may show utility in the treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease, embolism, thrombosis, atherosclerosis, aneurysm, or stroke. Moreover, the protein product of this gene is useful for the treatment and diagnosis of

5 hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in

10 lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as

15 a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:185 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1323 of SEQ ID NO:185, b is an integer of 15 to 1337, where both a and b correspond to the positions of nucleotide

25 residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 176**

30 The translation product of this gene shares sequence homology with both the RIC and MAT8 proteins (mouse), which are thought to be important in regulating



chloride conductance in cells by modulating the response mediated by cAMP and protein kinase C to extracellular signals.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

- 5 GTSLDAAATAASLSPRGCRRLRTPSSD (SEQ ID NO:1132),  
 QIQRHTRAPKQLIPLMTPRRSLRDHPQAQTSRQTPRPSSHLVFM RMTTPSSMM  
 NTPSGNGGCWSQLCCSSQASSSSPVASAGSCPGYAGIAGESIRNRS (SEQ ID  
 NO:1133), PRRSLRDHPQAQTSRQTPRPSSHLVFM (SEQ ID NO:1134),  
 THPPETGAVGRSCAVHHRHHHPHQWQVQAAVPVMPESLQVSPSETGADNXL
- 10 GTRRPSPLPAHRAQPPASPRRAWPEREDTDDEAGARAAGPSLLPPPTLPAPEG  
 YLAPWGLSLKLSPLL RQKV KHCGLC (SEQ ID NO:1135),  
 PESLQVSPSETGADNXLGTRRPSPLPAHRAQPPASP (SEQ ID NO:1136),  
 GTAPKAPGSLQGRAGLGEVGDS DRQPWLQLHHLCLPSLARLFEGMQEAGHG  
 ELAGGLVFGCPAGCQLLFLMDSPAMPA (SEQ ID NO:1137),
- 15 GEVGDS DRQPWLQLHHLCLPSLARLFEGMQEAGH (SEQ ID NO:1138),  
 GSGGLSGRLCLGMVSQRASWCHQWDELLWCSCVSLDLSLEAHPFLPVAGSG  
 SGVVVFHQQARLG LERWAGVLCRLHLGLVSGPECP (SEQ ID NO:1139),  
 and/or QWDELLWCSCVSLDLSLEAHPFLPVAGSGSGVVVFHQQARL (SEQ ID  
 NO:1140). Moreover, fragments and variants of these polypeptides (such as, for
- 20 example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by  
 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
 encoding these polypeptides) are encompassed by the invention. Antibodies that bind  
 polypeptides of the invention are also encompassed by the invention. Polynucleotides
- 25 encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

- This gene is expressed primarily in amniotic cells and hematopoietic cells
- 30 including macrophages, neutrophils, T cells, TNF induced aortic endothelium, and to  
 a lesser extent in testes, TNF induced epithelial cells, and smooth muscle.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly inflammatory responses mediated by T cells, macrophages, and/or neutrophils, particularly those involving TNF, and also cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 424 as residues: Thr-19 to Ala-33, Leu-54 to Asp-82, Pro-89 to Ala-97, Pro-100 to Lys-125, Ser-127 to Phe-135, Gly-164 to Leu-169, Cys-173 to Arg-178.

The tissue distribution in hematopoietic cells, combined with the homology to the RIC and mat-8 genes, indicates that the protein product of this gene is useful for modifying inflammatory responses to cytokines such as TNF, and thus modifying the duration and/or severity of inflammation. Polynucleotides and polypeptides derived from this gene are thought to be useful in the diagnosis and treatment of cancer. The protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and

in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:186 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 927 of SEQ ID NO:186, b is an integer of 15 to 941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 177**

This gene is expressed primarily in endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for  
20 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular disorders, including vascular restenosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
25 disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, endothelial, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative  
30 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial tissue indicates that the protein product of this gene is useful for treating diseases associated with vascular responses to injury such as vascular restenosis following angioplasty. Moreover, the protein product of this gene is useful for the treatment, detection, and/or prevention of a variety of other vascular disorders, which include, but are not limited to microvascular disease, embolism, thrombosis, atherosclerosis, aneurysm, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:187 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:187, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 178

This gene appears to be chimeric. There are two ORFs of interest. The first ORF-1 encodes a polypeptide preferably comprising one of the following polypeptide sequences:

MRPDWKAGAGPGGPPQKPAPSSQRKPPARPSAAAAAIAVAAAEERLRQR  
NRLRLEEDKPAVERCLEELVFGDVENDEALLRRLRGPRVQEHEDSGDSEVE  
NEAKGNFPPQKKPVWVDEEDEDEEMVDMMNRRFRKDMMKNASESKLSKD  
NLKKRLKEEFQHAMGGVPAWAETTKRKTSSDDESEDEDDLLQRTGNFISTS  
TSLPRGILKMKNQCQHANAERPTVARISICAVPSRCTDCDGCWD (SEQ ID  
NO:1141); and/or  
CLEELVFGDVENDEALLRRLRGPRVQEHEDSGDSEVENEAKGNFPPQKKPV

WVDEEDEDEEMVDMNNRFRKDMMKNA SESKLSKDNLKKRLKEEFQHAM  
GGVPAWAETTKRKTSSDDESEDEDDLLQRTGNFISTSTSLPRGILKMKNQC  
HANAERPTVARISICAVPSRCTDCDGC (SEQ ID NO:1142). The second ORF  
(ORF-2) encodes a polypeptide preferably comprising one of the following

5 polypeptide sequences:

LKEKIVRSFEVSPDGSFLLINGIAGYLHLLAMKTKELIGSMKINGRVAASTFSS  
DSKKVYASSGDGEVYVWDVNSRKCLNRFVDEGSLYGLSIATSRNGQYVACG  
SNCGVVNIYNQDSCLQETNPKPIKAIMNLVTGVTSLTFNPTTEILAIASEKMKE  
AVRLVHLPSC TVFSNFPVIKKNISHVHTMDFSPRSGYFALGNEKGKALMYR

10 LHHYSDF (SEQ ID NO:1143); and/or

KINGRVAASTFSSDSKKVYASSGDGEVYVWDVNSRKCLNRFVDEGSLYGLSI  
ATSRNGQYVACGSNCGVVNIYNQDSCLQETNPKPIKAIMNLVTGVTSLTFNP  
TTEILAIASEKMKEAVRLVHLPSC TVFSNFPVIKKNISHVHTMDFSPRSGYFA  
LGNEKGKAL (SEQ ID NO:1144).

15 In specific embodiments, polypeptides of the invention comprise, or alternatively  
consist of, the following amino acid sequences:

WLLGLDNAVSLFQVDGKTNPKIQSIYLERFPIFKACFSANGEEVLATSTH SKV  
LYVYD (SEQ ID NO:1145), LVFGDVENDE DALLRRLRGPRVQ (SEQ ID  
NO:1146), KNA SESKLSKDNLKKRLKEEFQHAMGGVP (SEQ ID NO:1147),

20 and/or SLPRGILKMKNQC HANAERPTVA (SEQ ID NO:1148). Moreover,  
fragments and variants of these polypeptides (such as, for example, fragments as  
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or  
99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
which hybridizes, under stringent conditions, to the polynucleotide encoding these  
25 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides  
of the invention are also encompassed by the invention. Polynucleotides encoding  
these polypeptides are also encompassed by the invention.

The translation product of this gene shares homology with the transcriptional  
repressor TUP1 of *Candida albicans* (See Genbank Accession No. gi|2245634  
30 (AF005741)), which is thought to modulate the expression levels of cellular filament  
and may implicate this protein as serving a useful role in the amelioration of  
proliferating cells and tissues.

This gene is expressed primarily in epididymus and endometrial tumors, and to a lesser extent, in T cell lymphoma and cell lines derived from colon cancer.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive or developmental conditions, which include tumors of the reproductive organs, including testis and endometrial cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 426 as residues: Ser-67 to Lys-72, Val-87 to Leu-93, Tyr-128 to Pro-141, Asp-204 to Gly-210.

The tissue distribution in reproductive tissue cancers, combined with the homology to a transcriptional repressor protein, indicates that the protein products of this gene are useful for treating tumors of the endometrium or epithelial tumors of the reproductive system. Moreover, the protein may also be useful as a contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:188 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1834 of SEQ ID NO:188, b is an integer of 15 to 1848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 179

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

MRILQLILLALATGLVGGETRIKGFECKLHSQPWQAALFEKTRLLCGATLIAP  
 RWLLTAAHCLKPRYIVHLGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKD  
 HRNDIMLVKMASPVSTITWAVRPLTLSSRCVTTAGTSCSFPAGAARPDPSYACLT  
 PCDAPTSPSLSTRSVRTPTPATSQTPWCVPACRKGARTPARVTPGALWSVTSL  
 FKALSPGARIRVRSPESLVSTRKSANMWTGSRRR (SEQ ID NO:1149);  
 ETRIKGFECKLHSQPWQAALFEKTRLLCGATLIAPRWLLTAAHCLKPRYIVH  
 LGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPVSTIT  
 WAVRPLTLSSRCVTTAGTSCSFPAGAARPDPSYACLTPCDAPTSPSLSTRSVRTP  
 TPATSQTPWCVPACRKGARTPARVTPGALWSVTSLFKALSPGARIRVRSPESL  
 VSTRKSANMWTGSRRR (SEQ ID NO:1150); and/or  
 CKLHSQPWQAALFEKTRLLCGATLIAPRWLLTAAHCLKPRYIVHLGQHNLQK  
 EEGCEQTRTATESFPHPGFNNS (SEQ ID NO:1151). Moreover, fragments and  
 variants of these polypeptides (such as, for example, fragments as described herein,  
 polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
 under stringent conditions, to the polynucleotide encoding these polypeptides) are  
 encompassed by the invention. Antibodies that bind polypeptides of the invention are  
 also encompassed by the invention. Polynucleotides encoding these polypeptides are  
 also encompassed by the invention.

The translation product of this gene shares sequence homology with neuropsin, a novel serine protease, which is thought to be important in modulating extracellular signaling pathways in the brain. Owing to the structural similarity to

other serine proteases, the protein products of this gene are expected to have serine protease activity which may be assayed by methods known in the art and described elsewhere herein. Moreover, this protein has been shown to also have homology to PSA (prostate specific antigen). PSA is a serum marker for prostate cancer and it is a member of the kallikrein family. The members of the kallikrein family are secreted serine proteases and some of them are good tissue specific markers. This new member of the kallikrein family has been detected twice in endometrial tumor cDNA library and therefore is a good candidate as a serum marker for endometrial tumor.

This gene is expressed primarily in endometrial tumor, and to a lesser extent, in colon cancer, benign hypertrophic prostate, and thymus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, or endocrine disorders, particularly cancers of the endometrium or colon and benign hypertrophy of the prostate. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital or reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, immune, endocrine, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 427 as residues: Glu-27 to Trp-35, Leu-77 to Ala-89, Pro-96 to Asn-109, Ser-149 to Arg-156, Gln-172 to Ile-182, Glu-193 to Gly-204, Glu-245 to Asn-250.

The tissue distribution in proliferative reproductive tissues, combined with the homology to serine proteases indicates that the protein product of this gene is useful for diagnosing, treating, and/or preventing hyperproliferative disorders such as cancer of the endometrium or colon and hyperplasia of the prostate. Similarly, expression



within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern  
5 formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:189 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1278 of SEQ ID NO:189, b is an integer of 15 to 1292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.

20

#### *FEATURES OF PROTEIN ENCODED BY GENE NO: 180*

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
25 VLQGRYFSPILEMRRLRPEGXXNLPGGSSRAQKEPRQDLTLVLWPHCPHFAMT  
RSYVPTKQCMVQGSFYCIFKGPVQNW (SEQ ID NO:1152), and/or CPRRRT  
CVRVEKSRPFQCQLHSIS (SEQ ID NO:1153). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
30 these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are

also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly neurodegenerative conditions, in addition to identifying and expanding stem cells in the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 428 as residues: Met-1 to Lys-9, Glu-26 to Lys-37, Lys-39 to Lys-48.

The tissue distribution in fetal brain indicates that the protein products of this gene are useful for detecting and expanding stem cell populations in the (or of the) central nervous system. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene

product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:190 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10           cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 892 of SEQ ID NO:190, b is an integer of 15 to 906, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 181**

In specific embodiments, polypeptides of the invention comprise, or alternatively  
20           consist of, the following amino acid sequences: PKEPGVPE (SEQ ID NO:1154), LQLKPRDPFSTLGPNVAVLSPQRLVLETLSKLSIQDNNVDLILATPPFSRLEKLY STMVRFSLDRKNPVCRRWLWYCWPTWLRGTAWQLVPLQCRRRAVSATSWAS (SEQ ID NO:1155), RDPFSTLGPNVAVLSPQRLVLETLSKLS (SEQ ID NO:1156), EVISGLFIQSRRRERGGQGVVGSHMILWGKSLFFFSPQRLTKNIFKNYSLLLTQR  
25           FLFPCETLLLQYVYSIRCTVQYMKGSTLYCTGLSSEQGLFTTANFLAPARL (SEQ ID NO:1157), and/or IRCTVQYMKGSTLYCTGLSSEQG (SEQ ID NO:1158). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
30           polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind

polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in early stage human brain, fetal liver/spleen, and stromal cells.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities, neural, immune, or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.,  
15 lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
20 NO: 429 as residues: Gln-42 to Gln-47, Gln-54 to Pro-60.

The tissue distribution in embryonic brain and fetal liver indicates that the protein products of this gene play a role in the development of the central nervous and hematopoietic systems. Therefore this gene and its products are useful for diagnosing or treating developmental abnormalities of the central nervous system. Moreover, the  
25 protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of  
30 neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in

the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:191 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1927 of SEQ ID NO:191, b is an integer of 15 to 1941, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 182

In specific embodiments, polypeptides of the invention comprise, or  
20 alternatively consists of, an amino acid sequence selected from the group:  
MPIDQVNPELHDFMQSAEVTIFALSWLITWFGHVLSDFRHVVRLYDFFLAC  
HPLMPIYFAAVIVLYREQEVLDCDCDMASVHHLLSQIPQDLPYETLISRKETFL  
FSFPHPNLLGRPLPNSKLRGRQPLLSKTLSTWHQPSRGLIWCCSGSGXRGLLRPE  
DRTKDVLTKPRTNRFVKLAVMGLTVALGAAALAVVKSALWAPKFQLQLFP  
25 (SEQ ID NO:1159; "ORF-1"); or  
CPEFFIPATLPCPFVFAFTSEASSRAYLTQRGPGGLAQNLMPPLPVGFWMGSLP  
PPWCWRKWVSEACSCFC (SEQ ID NO:1160; "ORF-2"). Moreover, fragments  
and variants of these polypeptides (such as, for example, fragments as described  
herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%  
30 identical to these polypeptides and polypeptides encoded by the polynucleotide which  
hybridizes, under stringent conditions, to the polynucleotide encoding these  
polypeptides) are encompassed by the invention. Antibodies that bind polypeptides

of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

ORF-2 is structurally similar to various TGF-beta family members. Thus, this polypeptide is expected to have a variety of activities in the modulation of cell growth and proliferation.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

CRQAGAVRGHPMFQTFYGVTXRFPVTRAAQAQQVAKAAASFRNPLPPTPG  
RWQRAHPKAHWERHKILCQAPRSPLCQVGSATGL (SEQ ID NO:1161),  
HILNYLMPIIDQVNPELHDFMQSAEVTIFALSWLITWFGHVLSDFRHVVRLY  
DFFLACHPLMPIYFAAVIVLYREQEVLDCDCDMASVHHLLSQIPQDLPYETLIS  
RXETFLFSFHPNLLGRPLPNSKLRGRQPLLSKTLWHQPSRGLIWCCGSGXR  
GLLRPEDRTKDVLTTPRTNRFVKLAVMGLTVALGAAALAVVKSALWAPKF  
QLQLFP (SEQ ID NO:1162), AEVGTIFALSWLITWFGHVLSDFRHVVRLYD  
(SEQ ID NO:1163), and/or VLTTPRTNRFVKLAVMGLTVALGAAALAVVKS  
(SEQ ID NO:1164). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 20.

This gene is expressed primarily in osteoclastoma, microvascular endothelium, and bone marrow derived cell lines.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal, vascular, or hematological diseases, particularly those involving aberrant

proliferation of stem cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, vascular, immune, hematological, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in

10 healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 430 as residues: Ser-33 to Ala-39.

The tissue distribution in bone marrow and endothelial cells indicates that the protein products of this gene is useful for treating disorders of the progenitors of the

15 immune system. Applications include in vivo expansion of progenitor cells, ex vivo expansion of progenitor cells, or the treatment of tumors of the circulatory system, such as lymphomas. Moreover, the protein product of this gene may also show utility in either the enhancement or inhibition of immune cell localization or targeting at sites of inflammation or injury. The protein product of this gene may be useful in the

20 treatment, detection, and/or prevention of a variety of vascular disorders, which include, but are not limited to microvascular disease, embolism, aneurysm, atherosclerosis, or stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:192 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2104 of SEQ ID NO:192, b is an

integer of 15 to 2118, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 183

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

GFSGVSAAGRRSGGTWQPQVQ (SEQ ID NO:1165), PGGLAVG SRW WSRSLT  
 10 (SEQ ID NO:1166), LEPSRQRRPRRRGGTSRPETDQRAKCWRQL (SEQ ID  
 NO:1167), VCLRCQNRMEN (SEQ ID NO:1168),  
 MAACTARRPGRGQPLVVPVADXGPVAKAALCAAXAGAFSPASTTTTRRHLS  
 SRNRPEGKVLETVG VFEVPKQNGKYETGQLFLHSIFGYRGVVLFPWQARLXD  
 RDVASAAPEKAENPAGHGSKEVKGKTHTYQVLIDARDCPHISQRSQTEAVT  
 15 FLANHDDSRALYAIPGLDYVSHEDILPYTSTDQVPIQHELPERFLLYDQTKAPP  
 FVARETLRAWQEKNHPWLELSDVHRETTENIRVTVIPFYMGMREAQNSHVY  
 WWRYCIRLENLDSDVVQLRERHWRFSLSGTLETVRGRGVVGREPVLSKEQP  
 AFQYSSHVSLQASSGHMWGTFRFERPDGSHFDVRIPFSLESNKDEKTPPSGL  
 HW (SEQ ID NO:1169), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA  
 20 (SEQ ID NO:1170), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ  
 ID NO:1171), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID  
 NO:1172), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID  
 NO:1173), MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID  
 NO:1174), VLETVG VFEVPKQNGKYETGQLFLHSIFGYRGVVL (SEQ ID  
 25 NO:1175), GLDYVSHEDILPYTST (SEQ ID NO:1176),  
 DVHRETTENIRVTVIPFYM (SEQ ID NO:1177),  
 WWRYCIRLENLDSDVVQLRER (SEQ ID NO:1178),  
 PAFQYSSHVSLQASSGHMWGTFRFER (SEQ ID NO:1179),  
 RLPCHKRRCFCLVIQKKSFKFMLDGNLISGGVGEDVFMADIVQAWDGIEGP  
 30 TVIMVSQEGHSFCLRLRYMWAVTSINQHLIVSVSFAFHLLGAMASRVLCFF  
 WSCRSHIPVXQSGLPKGQDDTSVAKNAMKEKLPGLIFSILFWHLKHTNCLQH  
 FALWSVSGREVPPRRRGRRWREGSSXGRAQSGLGHRAVSDRDHQRLPTAR



PPGCTGCHVPPERRPAADTEPNP (SEQ ID NO:1180),  
KEFMLDGNLISGGVGEDVFMADIVQAWDGIE (SEQ ID NO:1181),  
AVTSINQHLIVSVSFAFHLLGAMASRVLC (SEQ ID NO:1182), and/or  
TARPPGCTGCHVPPERRPAA (SEQ ID NO:1183). Moreover, fragments and  
5 variants of these polypeptides (such as, for example, fragments as described herein,  
polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to  
these polypeptides and polypeptides encoded by the polynucleotide which hybridizes,  
under stringent conditions, to the polynucleotide encoding these polypeptides) are  
encompassed by the invention. Antibodies that bind polypeptides of the invention are  
10 also encompassed by the invention. Polynucleotides encoding these polypeptides are  
also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome  
17. Accordingly, polynucleotides related to this invention are useful as a marker in  
linkage analysis for chromosome 17.

15 This gene is expressed primarily in gall bladder, prostate, and fetal brain, and  
to a lesser extent, in tumor and fetal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for  
differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
20 gastrointestinal, reproductive, neural, or growth related disorders such as cancers.  
Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
prostate, gall bladder, and fetal brain, expression of this gene at significantly higher or  
25 lower levels may be routinely detected in certain tissues or cell types (e.g.,  
gastrointestinal, reproductive, neural, developmental, and cancerous and wounded  
tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine,  
synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
30 the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

The tissue distribution in fetal brain and tumor tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of growth-related disorders, such as cancers. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival, in addition to metabolic, or reproductive disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:193 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1524 of SEQ ID NO:193, b is an integer of 15 to 1538, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.

30

**FEATURES OF PROTEIN ENCODED BY GENE NO: 184**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: SLCCPEGAEGC (SEQ ID NO:1184), QLKKTTHYDRPCP (SEQ ID NO:1185), QLKKTTHYDRPCP (SEQ ID NO:1186),  
5 MNRPCPFCLWKVFPLLLLHBEELFPLPVP (SEQ ID NO:1187), and/or KEKTFTPRNSLCCPEGAEGCIAGGDLQLKKTHY (SEQ ID NO:1188). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
10 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in stromal cell, tonsil, and glioblastoma.  
15 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immune and inflammatory disorders, in addition to neural disorders, such as glioblastoma. Similarly, polypeptides and antibodies directed to these  
20 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the stromal cells, tonsil, and glioblastoma expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and  
25 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.  
Additionally, it is believed that the product of this gene regulates pancreatic cell  
30 differentiation into beta cells. Accordingly, polynucleotides and polypeptides of the invention are useful in the treatment of insulin-dependent diabetes mellitus and

associated conditions e.g. pancreatic hypofunction and the prevention, as well as the treatment of undifferentiated type pancreatic cancers.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 432 as residues: Pro-27 to Ala-32.

- 5       The tissue distribution in stromal cells and tonsils indicates that the protein product of this gene is useful for diagnosis and treatment of immune and inflammatory disorders and glioblastoma. Similarly, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells
- 10       are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene
- 15       product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
- 20       Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:194 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
- 25       cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1084 of SEQ ID NO:194, b is an integer of 15 to 1098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14.
- 30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 185

This gene is expressed primarily in hepatocellular carcinoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic or metabolic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, metabolic, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 433 as residues: Gly-32 to Lys-39.

The tissue distribution in hepatocellular carcinoma tissue indicates that the protein product of this gene is useful for diagnosis and treatment of liver diseases. Moreover, the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the protein may have a useful role in treating, detecting, or preventing developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:195 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 987 of SEQ ID NO:195, b is an integer of 15 to 1001, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 186

10 This gene is expressed primarily in hippocampus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal or endocrine disorders, particularly behavioral and mood disorders.

15 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 434 as residues: Ser-14 to Tyr-20.

The tissue distribution in hippocampus indicates that the protein product of this gene is useful for the diagnosis and treatment of neuronal disorders. Moreover, the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, meningitis, encephalitis, demyelinating

diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:196 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1444 of SEQ ID NO:196, b is an integer of 15 to 1458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 187**

This gene is expressed primarily in bone cancer and hippocampus, and to a lesser extent, in osteoclastoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, bone-related disorders and neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, osteoclast, and hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, skeletal, and cancerous and  
5 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in hippocampus and skeletal tissues indicates that the  
10 protein product of this gene is useful for diagnosis and treatment of bone-related disorders and neuronal diseases. Similarly, this gene product is useful in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the  
15 diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Alternatively, the protein product of this gene is  
20 useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:197 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:197, b is an



integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 188

The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

10 This gene is expressed primarily in neuronal tissues such as hippocampus, spinal cord, and hypothalamus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
15 neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
20 types (e.g. neuronal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in neuronal tissues indicates that the protein product of this gene is useful for diagnosis and treatment of neuronal disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors,  
30 including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked

disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:198 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 937 of SEQ ID NO:198, b is an integer of 15 to 951, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 189**

The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

20 This gene is expressed primarily in neuronal tissues and immune tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal and immune-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal and immune-related tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. neuronal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such

a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 437 as residues: Pro-19 to Asp-25.

5           The tissue distribution neuronal and immune tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of neuronal and immune-related disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states, neuronal disorders, and behavioral disorders such as Alzheimer's  
10   Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of  
15   developmental disorders associated with the developing embryo, or sexually-linked disorders. Additionally, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as,  
20   antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial  
25   utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly  
30   available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:199 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1726 of SEQ ID NO:199, b is an integer of 15 to 1740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 190

10

The translation product of this gene shares sequence homology with human N33, a gene located in a homozygously deleted region of human metastatic prostate cancer, which is thought to be important in prevention of prostate cancer. The gene and its translation product also share sequence homology with an isolated

15 prostate/colon tumor suppressor gene (PSTG) product (WO9532214-A1.).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

AQRKKEMVLSEKVSQLEWTKRPMNGDKFRRLVKAPPRNYSVIVMFT  
ALQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFAMVDFDEGSDVFQML

20 NMNSAPTFINFPKKGPKRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPP  
NMAARWRFWCVSVT (SEQ ID NO:1189), MVVALLIVCDVPSAS (SEQ ID  
NO:1190), AQRKKEMVLSEKVSQLEWTKRPMNGDKF (SEQ ID NO:1191),  
MEWTKRPMNGDKFRRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNR

25 IFFA (SEQ ID NO:1193), MVDFDEGSDVFQMLNMNSAPTFINFPKKGPK (SEQ  
ID NO:1194), KRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPPN (SEQ ID  
NO:1195), and/or

YAGPLMLGLLAVIGGLVYLRRVIWNFSLIKLDGLLQLCVLCLL (SEQ ID

30 NO:1196). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in infant adrenal gland, prostate cell line, and to a lesser extent in adrenal gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer and endocrine disorders. Similarly, polypeptides and antibodies  
10 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and adrenal gland, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. prostate, endocrine, cancerous and wounded tissues) or  
15 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
20 NO: 438 as residues: Pro-34 to Gly-43, Arg-113 to Pro-120.

The tissue distribution infant adrenal gland, combined with the homology to N33 and prostate/colon tumor suppressor gene (PSTG) indicates that the protein product of this gene is useful for the diagnosis and treatment for prostate cancer and endocrine disorders, and that the nucleic acids and proteins of this gene can be used in  
25 the diagnosis and treatment of prostate, endocrine and colorectal cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:200 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1693 of SEQ ID NO:200, b is an integer of 15 to 1707, where both a and b correspond to the positions of nucleotide  
5 residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 191**

10 This gene is expressed primarily in T-cell, and to a lesser extent in fetal lung.  
Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and respiratory disorders. Similarly, polypeptides and antibodies directed to  
15 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, respiratory, cancerous and wounded tissues) or  
20 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
25 NO: 439 as residues: Trp-3 to Phe-9.

The tissue distribution in T-cells and fetal lung indicates that the protein product of this gene is useful for the diagnosis and treatment of immune and respiratory disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may  
30 also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor

marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. The tissue distribution also indicates that the protein product of this gene is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:201 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 765 of SEQ ID NO:201, b is an integer of 15 to 779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 192**

The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in

linkage analysis for chromosome 6. The translation product of this gene shares significant homology with the rat protein Neuritin, and in fact appears to be a human ortholog of the rat protein. It is believed that this gene is induced in rats by neural activity and neurotrophins, and that it promotes neuritogenesis. Neural activity and neurotrophins induce synaptic remodeling in part by altering gene expression. This gene is believed to be a glycosylphosphatidylinositol-anchored protein encoded by a hippocampal gene, and to possess neural activity. This molecule is believed to be expressed in post-mitotic differentiating neurons of the developing nervous system and neuronal structures associated with plasticity in the adult. Message of this gene is believed to be induced by neuronal activity and by the activity-regulated neurotrophins BDNF and NT-3. The product of this gene is believed to stimulate neurite outgrowth and arborization in primary embryonic hippocampal and cortical cultures, and to act as a downstream effector of activity-induced neurite outgrowth. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: DAVFKGFSDCLLKLGD (SEQ ID NO:1197), CQEGAKDMWDKLRKESKNLN (SEQ ID NO:1198), VLLVSLSAALATWLSF (SEQ ID NO:1199), MGLKLNGRYISLILAVQIAYLVQAVRAAGKCDVFKGFSDCLLKLGD (SEQ ID NO:1200), PAAWDDKTNIKTVCTYWEDFHSCVTALTDCQEGAKDMWDKLRKESKNLN IQGSLFELCGSGNGAAGSLLPAFPVLLVSLSAALATWLSF (SEQ ID NO:1201), and/or MGLKLNGRYISLILAVQIAYLVQAVRAAGKCDVFKGFSDCLLKLGDXXXXX PAAWDDKTNIKTVCTYWEDFHSCVTALTDCQEGAKDMWDKLRKESKN LNIQGSLFELCGSGNGAAGSLLPAFPVLLVSLSAALATWLSF (SEQ ID NO:1202). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.



This gene is expressed primarily in human placenta, endometrial tumor and tissues of the central nervous system (CNS).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to reproductive disorders, cancers and neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and neurological disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, neurological, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 440 as residues: Asp-47 to Asp-63, His-75 to Tyr-80, Pro-83 to Tyr-89.

The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive disorders such as endometrial tumors. Expression of this gene in tissues of the CNS, and its strong homology to Neuritin, suggest that the protein product from this gene is also useful in the treatment and diagnosis of neurological disorders and in the regeneration of neural tissues, e.g., following injury.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:202 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:202, b is an

integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 193

The translation product of this gene shares sequence homology with tenascin, which is thought to be important in development. The translation product of this gene is believed to be a ligand of the fibroblast growth factor family. FGF ligand activity is known in the art and can be assayed by methods known in the art and disclosed elsewhere herein.

Northern analysis indicates that a 2.5 kb band is expressed in brain and lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, growth disorders of the brain and lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer tissues, brain, lung, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, lung, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 441 as residues: Gly-29 to Glu-34, Arg-71 to Arg-76, Thr-176 to Cys-182, Gly-184 to Glu-199.

The tissue distribution in brain and lung, combined with the homology to tenascin indicates that the protein product of this gene is useful for diagnosis and treatment of cancers. Alternatively, given the tissue distribution indicated by Northern analysis, the translation product of this gene is thought to be a growth factor

functioning in the brain and lung that may be useful in treating neurodegeneration and lung disorder. For example, the protein product of this gene is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. Furthermore, the tissue  
5 distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division. Additionally, expression in the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It  
10 may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:203 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1960 of SEQ ID NO:203, b is an integer of 15 to 1974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 194**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
30 MNSAAGFSHLDRRERVCLKLGESFEKQPRCASTLC (SEQ ID NO:1203).  
Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,

97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides  
5 encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal human lung and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,  
10 lung development and respiratory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
15 tissues or cell types (e.g. respiratory, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution in fetal lung and neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of lung and immunity related diseases, for example, lung cancer, viral, fungal or bacterial infections (e.g. lesions caused by tuberculosis), inflammation (e.g. pneumonia), metabolic lesions etc. Furthermore, the tissue distribution indicates that the protein product of this gene  
25 is useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as  
30 well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:204 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1043 of SEQ ID NO:204, b is an integer of 15 to 1057, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 195**

This gene is expressed primarily in breast lymph node, and to a lesser extent in synovial tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and skeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast lymph node and synovium indicates that the protein product of this gene is useful for the diagnosis and treatment of immune and skeletal disorders. Furthermore, this gene product may be involved in the regulation

of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:205 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:205, b is an

integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 196

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5. The translation product of this gene shares  
 10 sequence homology with human M-phase phosphoprotein 4, which is thought to be important in the phosphorylation and signal transduction processes.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:  
 TIYPTEELQAVQKIVSITERALKLVSD (SEQ ID NO:1204),  
 15 RALKGVLRVGVLAAGLLLRGDRNVNLVLLC (SEQ ID NO:1205),  
 ALAALRHAKWFQARANGLQSCVIRILRDLCQRVPTWS (SEQ ID NO:1206),  
 GDALRRVFECISSGIL (SEQ ID NO:1207), LAFRQIHKVLGMDPLP (SEQ ID NO:1208), and/or  
 TIYPTEELQAVQKIVSITERALKLVSDSLSEHEKNKNKEGDDKKEGGKDRAL  
 20 KGVLRVGVLAAGLLLRGDRNVNLVLLCSEKPSKTLLSRIAENLPKQLAVISPE  
 KYDIKCAVSEAAIILNSCVEPKMQVTITLTSPHREENMREGDVTSGMVKDPPD  
 VLDRQKCLDALAALRHAKWFQARANGLQSCVIRILRDLCQRVPTWSDFPS  
 WAMELLVEKAISSASSPQSPGDALRRVFECISSGILKGSPGLLDPCFKDPFDL  
 ATMTDQQREDITSSAQFALRLLAFRQIHKVLGMDPLPQMSQRFNIHNNRKR  
 25 RDSGDGVDGFEEAGKKDKKDYDNF (SEQ ID NO:1209), MERHPKKKMCS  
 (SEQ ID NO:1210), and/or GENSSSDFPLFLFYFLVALASPPIFVSFIN (SEQ ID NO:1211). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by  
 30 the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind

polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human hippocampus, and to a lesser extent in prostate and human frontal cortex.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders related to the reproductive and nervous systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial  
15 fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
NO: 444 as residues: Arg-13 to Asp-21, Lys-28 to Lys-38, Val-76 to Asp-81, Ser-99  
20 to Ala-107, Pro-130 to Phe-136, Thr-143 to Ile-150, Pro-176 to Phe-182, Asn-186 to Gly-196, Ala-202 to Phe-214.

The tissue distribution in human hippocampus, prostate, and frontal cortex, combined with the homology to human M-phase phosphoprotein 4 indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive  
25 and nervous system disorders. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS;  
30 or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:206 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2451 of SEQ ID NO:206, b is an integer of 15 to 2465, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 197

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: MGSQHSAAARPSSCRRKQEDDRDG (SEQ ID NO:1212), LLAEREQEEAIAQFPYVEFTGRDSITCLTC (SEQ ID NO:1213), and/or QGTGYIPTEQVNELVALI PHSDQRLRPQRTKQYV (SEQ ID NO:1214). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human primary breast cancer, and to a lesser extent, in human adult spleen, Hodgkin's lymphoma I, and salivary gland.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, as well as immune disorders. Similarly, polypeptides and antibodies directed

to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly cancers and the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 445 as residues: Ser-126 to Gly-138.

The tissue distribution in tumors of breast origins indicates that the protein product of this gene is useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Furthermore, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:207 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1466 of SEQ ID NO:207, b is an integer of 15 to 1480, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 198**

This gene is expressed primarily in monocytes.

- 5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, blood cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
- 10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
- 15 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution in monocytes indicates that the protein product of this gene is useful for the diagnosis and treatment of blood cell disorders. Furthermore,
- 20 expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly
- 25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:208 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
- 30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:208, b is an

integer of 15 to 872, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 199

The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

10 This gene is expressed primarily in human ovary and synovia, and to a lesser extent in human 8 week whole embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in human ovary and human 8 week whole embryo indicates that the protein product of this gene is useful for the diagnosis and treatment of reproductive and developmental disorders. Similarly, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or

tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:209 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1765 of SEQ ID NO:209, b is an integer of 15 to 1779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 200**

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in  
20 linkage analysis for chromosome 8. The translation product of this gene shares limited sequence homology with collagen proline rich domain.

This gene is expressed primarily in CNS.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample  
25 and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at  
30 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample

taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID  
5 NO: 448 as residues: Pro-35 to Asp-41.

The tissue distribution in tissues of the central nervous system indicates that the protein product of this gene is useful for the diagnosis and treatment of neurological diseases and disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette's Syndrome, schizophrenia, mania, dementia,  
10 paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies  
15 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:210 and may have been publicly available prior to conception  
20 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2096 of SEQ ID NO:210, b is an  
25 integer of 15 to 2110, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 201

30

The translation product of this gene shares homology with a mammalian histone H1a protein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

ARLNVGRESLKREMLKSQGVKVSESPMGARHSSWPEGAAFCCKKVQGAQMQ  
FPPRR (SEQ ID NO:1215), ARLNVGRESLKREML (SEQ ID NO:1216), LKSQGV  
5 KVSSESPMGARHSSW (SEQ ID NO:1217), AFCKKVQGAQMVFPPRR (SEQ ID  
NO:1218), and/or AFCKKVQGAQMVFPPRR (SEQ ID NO:1219). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide  
10 which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention. (See Genbank Accession No. pir|S24178).

15 This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these  
20 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
25 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this  
30 gene is useful for the diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in vital immune functions. Therefore it may be also used as an agent for immunological

disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Protein, as well as, antibodies directed against the protein may show utility as a tumor  
5 marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:211 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
10 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:211, b is an integer of 15 to 938, where both a and b correspond to the positions of nucleotide  
15 residues shown in SEQ ID NO:211, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 202**

20 This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these  
25 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
30 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene



expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:212 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1537 of SEQ ID NO:212, b is an integer of 15 to 1551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 203

25

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infectious disorders, immune disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or  
5 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 451 as residues: Thr-31 to Lys-36.

10 The tissue distribution in neutrophils indicates that the protein product of this gene is useful for the diagnosis and treatment of infectious disorders, immune disorders, and cancers. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
15 deficiency diseases such as AIDS, and leukemia. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:213 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is  
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 983 of SEQ ID NO:213, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 204

The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16. The translation product of this gene shares  
5 sequence homology with lactate dehydrogenase, which is thought to be important in lactate metabolism.

This gene is expressed primarily in human tonsils, and to a lesser extent, in spleen, and neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for  
10 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, infectious disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
15 disorders of the above tissues or cells, particularly of the immune disorders, infectious disorders, and cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. tonsils, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
20 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 452 as residues: Gly-7 to Ser-12.

25 The tissue distribution in human tonsils, spleen, and neutrophils, combined with the homology to lactate dehydrogenase gene indicates that the protein product of this gene is useful for the diagnosis and treatment of immune disorders, infectious disorders, and cancers. Furthermore, expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or  
30 activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of

cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:214 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1482 of SEQ ID NO:214, b is an integer of 15 to 1496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 205

The translation product of this gene shares sequence homology with Gcap1 protein which is developmentally regulated in brain.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:  
NFFFVCLFKSSLRLVNSSYTPILCVL (SEQ ID NO:1220). Moreover, fragments and variants of this polypeptide (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridize, under stringent conditions, to the polynucleotide encoding this polypeptide are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding this polypeptide are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

10 This gene is expressed primarily in placenta and endometrial tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vasculogenesis/angiogenesis and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. placental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 453 as residues: Lys-9 to Gln-16.

The tissue distribution placenta and endometrial tumors, combined with the homology to Gcap1 protein indicates that the protein product of this gene is useful for the diagnosis and treatment of disorders or dysfunctions of the vascular system, which include, but are not limited to atherosclerosis, hypertension, embolism, thrombosis, microvascular disease, aneurysm, or stroke, or tumorigenesis. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta

indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:215 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1294 of SEQ ID NO:215, b is an integer of 15 to 1308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 206

25

The translation product of this gene shares sequence homology with a *C. elegans* protein of unknown function (F23B2.4 [*Caenorhabditis elegans*]).

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequences:

30 VQVLEQLTNNVAESRFNDAAYYYWMLSMQCLDIAQD (SEQ ID NO:1221),  
PAQKDTMLGKFYHFQRLAELYHGYHAIHRHTEDP (SEQ ID NO:1222),  
LAKQSKALGAYRLARHAYDKLRGLYIP (SEQ ID NO:1223),

ARFQKSIELGTLTIRAKPFHDSEELVPLCYRCSTNN (SEQ ID NO:1224),  
PLLNNLGNVCINCRQPFIFSASSYDVLHLVEFYLEEGITDEEAISLIDLEVLRPK  
RDDRQLEICKQQLPDSCG (SEQ ID NO:1225)  
MPYAQWLAENDRFEEAQKAFHKAGRQREA (SEQ ID NO:1226), and/or  
5 FSVHRPETLFNISRFLHSLPKDTPSGISKVKILFT (SEQ ID NO:1227).  
Moreover, fragments and variants of these polypeptides (such as, for example,  
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the  
polynucleotide which hybridizes, under stringent conditions, to the polynucleotide  
10 encoding these polypeptides) are encompassed by the invention. Antibodies that bind  
polypeptides of the invention are also encompassed by the invention. Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes.

Polynucleotides and polypeptides of the invention are useful as reagents for  
15 differential identification of the tissue(s) or cell type(s) present in a biological sample  
and for diagnosis of diseases and conditions which include, but are not limited to,  
male reproductive and endocrine disorders. Similarly, polypeptides and antibodies  
directed to these polypeptides are useful in providing immunological probes for  
differential identification of the tissue(s) or cell type(s). For a number of disorders of  
20 the above tissues or cells, particularly of the reproductive and endocrine systems,  
expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues or cell types (e.g. testes, cancerous and wounded tissues)  
or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and  
spinal fluid) or another tissue or cell sample taken from an individual having such a  
25 disorder, relative to the standard gene expression level, i.e., the expression level in  
healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes indicates that the protein product of this gene  
is useful for the treatment of male reproductive and endocrine disorders.

Furthermore, the tissue distribution indicates that the protein product of this gene is  
30 useful for the treatment and diagnosis of conditions concerning proper testicular  
function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore,  
this gene product is useful in the treatment of male infertility and/or impotence. This

gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed,  
5 particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly  
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:216 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1691 of SEQ ID NO:216, b is an integer of 15 to 1705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 207**

This gene is expressed in fetal lung.

25 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, lung diseases such as cystic fibrosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
30 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell



types (e.g. respiratory, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
5 having the disorder.

Predicted epitopes include those comprising a sequence shown in SEQ ID NO: 455 as residues: Tyr-49 to Cys-54.

The tissue distribution in fetal lung indicates that the protein product of this gene is useful for the detection and treatment of disorders associated with developing  
10 lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that the protein product of this gene is useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
15 and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:217 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
20 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 985 of SEQ ID NO:217, b is an integer of 15 to 999, where both a and b correspond to the positions of nucleotide  
25 residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.

Table 1

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|----------------------------|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 1        | HLHDS67       | 97979 03/27/97             | Uni-ZAP XR    | 11              | 2526          | 427                 | 2526                | 458                  | 458                             | 249             | 1                   | 30                 | 31                           | 30             |
| 2        | HLHDZ58       | 97979 03/27/97             | Uni-ZAP XR    | 12              | 1131          | 1                   | 1131                | 129                  | 129                             | 250             | 1                   | 14                 | 15                           | 115            |
| 3        | HLMMJ13       | 97979 03/27/97             | Lambda ZAP II | 13              | 941           | 39                  | 941                 | 62                   | 62                              | 251             | 1                   | 44                 | 45                           | 102            |
| 3        | HLMMJ13       | 97979 03/27/97             | Lambda ZAP II | 218             | 941           | 39                  | 941                 | 245                  | 245                             | 456             | 1                   | 35                 | 36                           | 41             |
| 4        | HLTEI25       | 97979 03/27/97             | Uni-ZAP XR    | 14              | 843           | 1                   | 843                 | 155                  | 155                             | 252             | 1                   | 19                 | 20                           | 42             |
| 5        | HMSJX24       | 97979 03/27/97             | Uni-ZAP XR    | 15              | 1018          | 1                   | 1018                | 90                   | 90                              | 253             | 1                   | 18                 | 19                           | 36             |
| 6        | HNFD65        | 97979 03/27/97             | Uni-ZAP XR    | 16              | 661           | 1                   | 661                 | 76                   | 76                              | 254             | 1                   | 28                 | 29                           | 127            |
| 7        | HNHDX07       | 97979 03/27/97             | Uni-ZAP XR    | 17              | 553           | 1                   | 553                 | 106                  | 106                             | 255             | 1                   | 23                 | 24                           | 66             |
| 8        | HNHGC82       | 97979 03/27/97             | Uni-ZAP XR    | 18              | 869           | 1                   | 869                 | 101                  | 101                             | 256             | 1                   | 21                 | 22                           | 68             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|----------------------------|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 9        | HNHGO09       | 97979 03/27/97             | Uni-ZAP XR    | 19              | 959           | 1                   | 959                 | 176                  | 176                             | 257             | 1                   | 21                 | 22                           | 43             |
| 10       | HOUBE18       | 97979 03/27/97             | Uni-ZAP XR    | 20              | 1446          | 1                   | 1446                | 101                  | 101                             | 258             | 1                   | 27                 | 28                           | 50             |
| 11       | HOUDL69       | 97979 03/27/97             | Uni-ZAP XR    | 21              | 1471          | 579                 | 1460                | 692                  | 692                             | 259             | 1                   | 31                 | 32                           | 42             |
| 12       | HPMFI71       | 97979 03/27/97             | Uni-ZAP XR    | 22              | 1402          | 242                 | 1402                | 401                  | 401                             | 260             | 1                   | 32                 | 33                           | 60             |
| 13       | HPMGQ55       | 97979 03/27/97             | Uni-ZAP XR    | 23              | 1047          | 1                   | 1047                | 164                  | 164                             | 261             | 1                   | 26                 | 27                           | 35             |
| 14       | HPQAC69       | 97979 03/27/97             | Lambda ZAP II | 24              | 990           | 1                   | 988                 | 82                   | 82                              | 262             | 1                   | 20                 | 21                           | 37             |
| 15       | HPTBB03       | 97979 03/27/97             | Uni-ZAP XR    | 25              | 1208          | 350                 | 1173                | 398                  | 398                             | 263             | 1                   | 29                 | 30                           | 210            |
| 16       | HPTWA66       | 97979 03/27/97             | pBluescript   | 26              | 1922          | 1381                | 1922                | 24                   | 24                              | 264             | 1                   | 33                 | 34                           | 547            |
| 16       | HPTWA66       | 97979 03/27/97             | pBluescript   | 219             | 575           | 1                   | 575                 | 148                  | 148                             | 457             | 1                   | 22                 | 23                           | 65             |
| 17       | HPTWC08       | 97979 03/27/97             | pBluescript   | 27              | 1951          | 1422                | 1874                | 219                  | 219                             | 265             | 1                   | 19                 | 20                           | 299            |
| 18       | HRGCZ46       | 97979 03/27/97             | Uni-ZAP XR    | 28              | 3989          | 2635                | 3989                |                      | 2748                            | 266             | 1                   | 16                 | 17                           | 39             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 19       | HSAVU34       | 97979<br>03/27/97                       | Uni-ZAP XR | 29              | 3735          | 2966                | 3735                | 272                  | 272                             | 267             | 1                   | 30                 | 31                           | 594            |
| 19       | HSAVU34       | 97979<br>03/27/97                       | Uni-ZAP XR | 220             | 3018          | 1929                | 3018                | 26                   | 26                              | 458             | 1                   | 1                  | 2                            | 156            |
| 20       | HSDFW61       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 30              | 1667          | 59                  | 1625                | 138                  | 138                             | 268             | 1                   | 32                 | 33                           | 130            |
| 21       | HSDGP60       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 31              | 1408          | 1                   | 1408                | 285                  | 285                             | 269             | 1                   |                    |                              | 20             |
| 22       | HSOAJ55       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 32              | 3186          | 2402                | 3186                | 302                  | 302                             | 270             | 1                   | 43                 | 44                           | 159            |
| 22       | HSOAJ55       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 221             | 2031          | 1273                | 2031                | 1285                 | 1285                            | 459             | 1                   | 29                 | 30                           | 30             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 23       | HSQE084       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 33              | 971           | 13                  | 971                 | 91                   | 91                              | 271             | 1                   | 19                 | 20                           | 218            |
| 23       | HSQE084       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 222             | 968           | 8                   | 968                 | 86                   | 86                              | 460             | 1                   | 20                 | 21                           | 56             |
| 24       | HSXAM05       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 34              | 1792          | 369                 | 1792                | 470                  | 470                             | 272             | 1                   | 26                 | 27                           | 49             |
| 25       | HSXAS67       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 35              | 896           | 1                   | 896                 | 96                   | 96                              | 273             | 1                   | 32                 | 33                           | 121            |
| 26       | HTDAF28       | 97974<br>04/04/97<br>209080<br>05/29/97 | pSport1    | 36              | 912           | 1                   | 912                 | 38                   | 38                              | 274             | 1                   | 22                 | 23                           | 87             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector      | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 27       | HTEGQ64       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 37              | 1382          | 67                  | 1382                | 271                  | 271                             | 275             | 1                   |                    |                              | 25             |
| 28       | HTGEU09       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 38              | 872           | 1                   | 872                 | 74                   | 74                              | 276             | 1                   | 18                 | 19                           | 28             |
| 29       | HTOAM21       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 39              | 812           | 1                   | 812                 | 41                   | 41                              | 277             | 1                   | 30                 | 31                           | 43             |
| 30       | HTPBW79       | 209511<br>12/03/97                      | Uni-ZAP XR  | 40              | 1515          | 118                 | 1507                | 302                  | 302                             | 278             | 1                   | 24                 | 25                           | 362            |
| 30       | HTSEV09       | 97974<br>04/04/97<br>209080<br>05/29/97 | pBluescript | 223             | 1404          | 1                   | 1265                | 92                   | 92                              | 461             | 1                   | 19                 | 20                           | 415            |
| 31       | HIPCD40       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 41              | 704           | 22                  | 704                 |                      | 117                             | 279             | 1                   | 18                 | 19                           | 127            |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 32       | HTWBY48       | 97974<br>04/04/97<br>209080<br>05/29/97 | pSport1    | 42              | 1094          | 1                   | 1094                | 32                   | 32                              | 280             | 1                   | 34                 | 35                           | 53             |
| 33       | HTWCI46       | 97974<br>04/04/97<br>209080<br>05/29/97 | pSport1    | 43              | 1821          | 892                 | 1647                | 56                   | 56                              | 281             | 1                   | 26                 | 27                           | 29             |
| 34       | HTXGI75       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 44              | 1024          | 30                  | 1024                |                      | 167                             | 282             | 1                   | 20                 | 21                           | 25             |
| 35       | HWTBFS9       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 45              | 983           | 779                 | 983                 | 85                   | 85                              | 283             | 1                   | 30                 | 31                           | 221            |
| 35       | HWTBFS9       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 224             | 707           | 488                 | 707                 | 514                  | 514                             | 462             | 1                   | 41                 | 42                           | 64             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 36       | HADAE74       | 97974<br>04/04/97<br>209080<br>05/29/97 | pSport1    | 46              | 2421          | 664                 | 1587                | 2110                 | 2110                            | 284             | 1                   | 33                 | 34                           | 40             |
| 37       | HAGFB60       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 47              | 840           | 1                   | 840                 | 97                   | 97                              | 285             | 1                   | 30                 | 31                           | 48             |
| 38       | HATEF60       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 48              | 2432          | 1193                | 2246                | 1491                 | 1491                            | 286             | 1                   | 17                 | 18                           | 51             |
| 39       | HBMSN25       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 49              | 1742          | 1165                | 1742                | 1207                 | 1207                            | 287             | 1                   | 23                 | 24                           | 31             |
| 40       | HCDAR68       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR | 50              | 1487          | 181                 | 1455                | 325                  | 325                             | 288             | 1                   | 35                 | 36                           | 56             |



| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector      | NT SEQ ID NO: X | NT Total Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 41       | HCE3J79       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 51              | 1328          | 251                 | 1328                | 525                  | 525                             | 289             | 1                   |                    |                              | 21             |
| 42       | HMDAN54       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 52              | 1856          | 725                 | 1853                | 928                  | 928                             | 290             | 1                   | 33                 | 34                           | 50             |
| 43       | HCECA49       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 53              | 1558          | 310                 | 1408                | 109                  | 109                             | 291             | 1                   | 30                 | 31                           | 98             |
| 44       | HCEEC15       | 97974<br>04/04/97<br>209080<br>05/29/97 | Uni-ZAP XR  | 54              | 948           | 1                   | 948                 | 9                    | 9                               | 292             | 1                   | 23                 | 24                           | 65             |
| 45       | HCESF40       | 97974<br>04/04/97<br>209080<br>05/29/97 | pBluescript | 55              | 990           | 99                  | 990                 | 193                  | 193                             | 293             | 1                   | 32                 | 33                           | 256            |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 45       | HCESF40       | 97974<br>04/04/97<br>209080<br>05/29/97 | pBluescript   | 225             | 1384          | 99                  | 1384                | 193                  | 193                             | 463             | 1                   | 32                 | 33                           | 205            |
| 46       | HCFMV39       | 97974<br>04/04/97<br>209080<br>05/29/97 | pSport1       | 56              | 1603          | 1                   | 1296                | 96                   | 96                              | 294             | 1                   | 29                 | 30                           | 102            |
| 47       | HCMSX86       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR    | 57              | 1052          | 5                   | 786                 | 12                   | 12                              | 295             | 1                   | 28                 | 29                           | 32             |
| 48       | HCNAP62       | 97975<br>04/04/97<br>209081<br>05/29/97 | Lambda ZAP II | 58              | 814           | 1                   | 558                 | 93                   | 93                              | 296             | 1                   | 22                 | 23                           | 42             |
| 49       | HCRAF32       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR    | 59              | 1215          | 257                 | 1215                |                      | 356                             | 297             | 1                   | 19                 | 20                           | 20             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector        | NT SEQ ID NO: X | NT Total Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 50       | HCUDC07       | 97975<br>04/04/97<br>209081<br>05/29/97 | ZAP Express   | 60              | 478           | 1                   | 478                 | 147                  | 147                             | 298             | 1                   | 36                 | 37                           | 69             |
| 51       | HCWBB42       | 97975<br>04/04/97<br>209081<br>05/29/97 | ZAP Express   | 61              | 618           | 1                   | 618                 | 212                  | 212                             | 299             | 1                   | 35                 | 36                           | 74             |
| 52       | HDTAB05       | 97975<br>04/04/97<br>209081<br>05/29/97 | pCMVSPORT 2.0 | 62              | 751           | 1                   | 751                 | 257                  | 257                             | 300             | 1                   | 21                 | 22                           | 32             |
| 53       | HE2AV74       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR    | 63              | 780           | 283                 | 780                 |                      | 433                             | 301             | 1                   |                    |                              | 16             |
| 54       | HE2AY71       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR    | 64              | 588           | 21                  | 588                 | 169                  | 169                             | 302             | 1                   |                    |                              | 16             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 5' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 55       | HE2GS36       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 65              | 945           | 1                   | 349                 | 520                  | 520                             | 303             | 1                   | 39                 | 40                           | 111            |
| 55       | HE2GS36       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 226             | 774           | 272                 | 774                 | 445                  | 445                             | 464             | 1                   |                    |                              | 37             |
| 56       | HE2OF09       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 66              | 1866          | 1313                | 1866                | 1596                 | 1596                            | 304             | 1                   |                    |                              | 11             |
| 57       | HE6EU50       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 67              | 1152          | 117                 | 686                 | 237                  | 237                             | 305             | 1                   | 20                 | 21                           | 34             |
| 58       | HE9HU17       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 68              | 2483          | 1577                | 2448                | 1620                 | 1620                            | 306             | 1                   |                    |                              | 14             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 59       | HE9ND48       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 69              | 536           | 1                   | 536                 | 83                   | 83                              | 307             | 1                   | 36                 | 37                           | 43             |
| 60       | HEBBW11       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 70              | 574           | 97                  | 564                 | 109                  | 109                             | 308             | 1                   | 55                 | 56                           | 137            |
| 60       | HEBBW11       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 227             | 865           | 647                 | 865                 |                      | 388                             | 465             | 1                   | 30                 | 31                           | 135            |
| 61       | HELDY74       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 71              | 932           | 1                   | 932                 | 201                  | 201                             | 309             | 1                   | 17                 | 18                           | 33             |
| 62       | HEMAE80       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR | 72              | 996           | 1                   | 945                 | 12                   | 12                              | 310             | 1                   | 24                 | 25                           | 136            |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector      | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 63       | HFEBA88       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR  | 73              | 785           | 464                 | 785                 | 356                  | 356                             | 311             | 1                   | 29                 | 30                           | 57             |
| 64       | HFGAB89       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR  | 74              | 1069          | 196                 | 1047                | 295                  | 295                             | 312             | 1                   | 32                 | 33                           | 34             |
| 65       | HFVHY45       | 97975<br>04/04/97<br>209081<br>05/29/97 | pBluescript | 75              | 831           | 1                   | 831                 | 50                   | 50                              | 313             | 1                   | 36                 | 37                           | 89             |
| 66       | HGBAJ93       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR  | 76              | 590           | 1                   | 590                 | 233                  | 233                             | 314             | 1                   | 38                 | 39                           | 94             |
| 67       | HGBBQ69       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR  | 77              | 1274          | 1                   | 1273                | 105                  | 105                             | 315             | 1                   | 24                 | 25                           | 43             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date     | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--------------------------------|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 68       | HHFCF08       | 97975 04/04/97 209081 05/29/97 | Uni-ZAP XR    | 78              | 1133          | 4                   | 1042                | 175                  | 175                             | 316             | 1                   | 23                 | 24                           | 30             |
| 69       | HHFHJ59       | 97975 04/04/97 209081 05/29/97 | Uni-ZAP XR    | 79              | 661           | 1                   | 661                 | 192                  | 192                             | 317             | 1                   | 29                 | 30                           | 112            |
| 70       | HHFHR32       | 97975 04/04/97 209081 05/29/97 | Uni-ZAP XR    | 80              | 1378          | 1                   | 1378                | 58                   | 58                              | 318             | 1                   | 25                 | 26                           | 235            |
| 71       | HHGCN69       | 97975 04/04/97 209081 05/29/97 | Lambda ZAP II | 81              | 1440          | 298                 | 1440                | 532                  | 532                             | 319             | 1                   | 23                 | 24                           | 34             |
| 72       | HHGDO13       | 97975 04/04/97 209081 05/29/97 | Lambda ZAP II | 82              | 1381          | 766                 | 1371                | 993                  | 993                             | 320             | 1                   | 23                 | 24                           | 34             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 5' NT of Clone Seq. | 5' NT of 5' NT Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|---------------|-----------------|---------------|---------------------|---------------------|----------------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 73       | HHPFD63       | 97975<br>04/04/97<br>209081<br>05/29/97 | Uni-ZAP XR    | 83              | 1706          | 182                 | 1644                | 257                        | 257                             | 321             | 1                   | 24                 | 25                           | 81             |
| 74       | HHSEG23       | 97976<br>04/04/97                       | Uni-ZAP XR    | 84              | 573           | 1                   | 573                 | 160                        | 160                             | 322             | 1                   | 18                 | 19                           | 71             |
| 75       | HLPV06        | 97976<br>04/04/97                       | Uni-ZAP XR    | 85              | 684           | 199                 | 684                 | 323                        | 323                             | 323             | 1                   | 27                 | 28                           | 33             |
| 76       | HKIXL73       | 97976<br>04/04/97                       | pBluescript   | 86              | 1036          | 591                 | 1036                | 690                        | 690                             | 324             | 1                   | 32                 | 33                           | 114            |
| 77       | HKMNC43       | 97976<br>04/04/97                       | pBluescript   | 87              | 908           | 1                   | 908                 | 139                        | 139                             | 325             | 1                   | 18                 | 19                           | 108            |
| 78       | HMEJE31       | 97976<br>04/04/97                       | Lambda ZAP II | 88              | 655           | 1                   | 655                 | 165                        | 165                             | 326             | 1                   | 33                 | 34                           | 64             |
| 79       | HMSKS35       | 97976<br>04/04/97                       | Uni-ZAP XR    | 89              | 1102          | 1                   | 1102                | 228                        | 228                             | 327             | 1                   | 23                 | 24                           | 49             |
| 79       | HMSKS35       | 97976<br>04/04/97                       | Uni-ZAP XR    | 228             | 1102          | 1                   | 1102                | 228                        | 228                             | 466             | 1                   | 26                 | 27                           | 49             |
| 80       | HNF AE54      | 97976<br>04/04/97                       | Uni-ZAP XR    | 90              | 1533          | 665                 | 1518                | 347                        | 347                             | 328             | 1                   | 26                 | 27                           | 293            |
| 81       | HNFJH45       | 97976<br>04/04/97                       | Uni-ZAP XR    | 91              | 575           | 1                   | 575                 | 275                        | 275                             | 329             | 1                   | 30                 | 31                           | 67             |



| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 82       | HNGBT31       | 97976<br>04/04/97                       | Uni-ZAP XR    | 92              | 639           | 1                   | 639                 | 224                  | 224                             | 330             | 1                   | 28                 | 29                           | 104            |
| 83       | HNGIN60       | 97976<br>04/04/97                       | Uni-ZAP XR    | 93              | 858           | 1                   | 858                 | 239                  | 239                             | 331             | 1                   | 23                 | 24                           | 58             |
| 83       | HNGIN60       | 97976<br>04/04/97                       | Uni-ZAP XR    | 229             | 744           | 1                   | 744                 | 225                  | 225                             | 467             | 1                   | 43                 | 44                           | 70             |
| 84       | HNGJG84       | 97976<br>04/04/97                       | Uni-ZAP XR    | 94              | 526           | 1                   | 526                 | 268                  | 268                             | 332             | 1                   | 29                 | 30                           | 38             |
| 85       | HNHDW42       | 97976<br>04/04/97                       | Uni-ZAP XR    | 95              | 426           | 1                   | 426                 | 168                  | 168                             | 333             | 1                   | 28                 | 29                           | 71             |
| 86       | HNHFL57       | 97976<br>04/04/97                       | Uni-ZAP XR    | 96              | 844           | 1                   | 844                 | 98                   | 98                              | 334             | 1                   | 25                 | 26                           | 61             |
| 87       | HOGAR52       | 97977<br>04/04/97<br>209082<br>05/29/97 | pCMVSPORT 2.0 | 97              | 1985          | 453                 | 1985                | 533                  | 533                             | 335             | 1                   | 17                 | 18                           | 285            |
| 88       | HOSBZ55       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 98              | 1416          | 69                  | 1416                | 246                  | 246                             | 336             | 1                   | 32                 | 33                           | 54             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector          | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-----------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 89       | HOSDI92       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR      | 99              | 1760          | 1469                | 1760                | 934                  | 934                             | 337             | 1                   | 22                 | 23                           | 59             |
| 89       | HOSDI92       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR      | 230             | 1935          | 141                 | 772                 |                      | 274                             | 468             | 1                   | 20                 | 21                           | 58             |
| 90       | HPBCU51       | 97977<br>04/04/97<br>209082<br>05/29/97 | pBluescript SK- | 100             | 599           | 1                   | 599                 | 86                   | 86                              | 338             | 1                   | 27                 | 28                           | 119            |
| 91       | HPCAL49       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR      | 101             | 784           | 1                   | 784                 | 113                  | 113                             | 339             | 1                   | 36                 | 37                           | 38             |
| 92       | HPFCR13       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR      | 102             | 404           | 1                   | 404                 | 266                  | 266                             | 340             | 1                   | 30                 | 31                           | 46             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 92       | HPFCR13       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 231             | 1035          | 602                 | 1035                | 859                  | 859                             | 469             | 1                   | 32                 | 33                           | 58             |
| 93       | HPHAC83       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 103             | 2218          | 840                 | 2182                | 1035                 | 1035                            | 341             | 1                   | 17                 | 18                           | 17             |
| 93       | HOENZ45       | 209568<br>01/06/98                      | pCMVSPORT 2.0 | 232             | 760           | 1                   | 728                 | 86                   | 86                              | 470             | 1                   | 36                 | 37                           | 61             |
| 94       | HPMBQ32       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 104             | 1351          | 1                   | 1351                | 18                   | 18                              | 342             | 1                   | 23                 | 24                           | 86             |
| 95       | HPWAN23       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 105             | 2066          | 51                  | 2052                | 270                  | 270                             | 343             | 1                   | 29                 | 30                           | 537            |
| 95       | HPWAN23       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR    | 233             | 2057          | 1                   | 1954                | 220                  | 220                             | 471             | 1                   | 29                 | 30                           | 315            |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date             | Vector      | NT SEQ ID NO: X | NT Total Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 96       | HRDFB85       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR  | 106             | 1705          | 23                  | 1697                | 233                  | 233                             | 344             | 1                   | 21                 | 22                           | 201            |
| 97       | HRGBR28       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR  | 107             | 1167          | 1                   | 557                 | 604                  | 604                             | 345             | 1                   | 22                 | 23                           | 122            |
| 98       | HSKGN81       | 97977<br>04/04/97<br>209082<br>05/29/97 | pBluescript | 108             | 1907          | 151                 | 1432                | 353                  | 353                             | 346             | 1                   | 23                 | 24                           | 260            |
| 98       | HSKGN81       | 97977<br>04/04/97<br>209082<br>05/29/97 | pBluescript | 234             | 2084          | 335                 | 2084                | 537                  | 537                             | 472             | 1                   | 19                 | 20                           | 23             |
| 99       | HSPAH56       | 97977<br>04/04/97<br>209082<br>05/29/97 | pSport1     | 109             | 611           | 1                   | 576                 | 229                  | 229                             | 347             | 1                   | 25                 | 26                           | 47             |
| 100      | HB8EU04       | 209746<br>04/07/98                      | Uni-ZAP XR  | 110             | 2632          | 294                 | 2632                | 337                  | 337                             | 348             | 1                   | 25                 | 26                           | 333            |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 100      | HSXBT86       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR | 235             | 2143          | 53                  | 1096                | 235                  | 235                             | 473             | 1                   |                    |                              | 9              |
| 101      | HSXCS62       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR | 111             | 2249          | 1                   | 1953                | 90                   | 90                              | 349             | 1                   | 18                 | 19                           | 199            |
| 102      | HTEFU09       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR | 112             | 2198          | 228                 | 2158                | 400                  | 400                             | 350             | 1                   |                    |                              | 23             |
| 103      | HTEKM35       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR | 113             | 1043          | 40                  | 1043                | 320                  | 320                             | 351             | 1                   | 20                 | 21                           | 142            |
| 104      | HTGEP89       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR | 114             | 703           | 1                   | 703                 | 285                  | 285                             | 352             | 1                   | 29                 | 30                           | 94             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date              | Vector      | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|---|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 105      | HTGEW91       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR  | 115             | 3684          | 526                 | 1338                | 584                  | 584                             | 353             | 1                   | 24                 | 25                           | 37             |
| 106      | HTOEY16       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR  | 116             | 1965          | 127                 | 1915                | 202                  | 202                             | 354             | 1                   | 27                 | 28                           | 38             |
| 107      | HTPCN79       | 97977<br>04/04/97<br>209082<br>05/29/97 | Uni-ZAP XR  | 117             | 503           | 1                   | 503                 |                      | 1                               | 355             | 1                   | 7                  | 8                            | 70             |
| 108      | HTSGM54       | 97977<br>04/04/97<br>209082<br>05/29/97 | pBluescript | 118             | 1071          | 50                  | 981                 | 29                   | 29                              | 356             | 1                   | 30                 | 31                           | 227            |
| 108      | HTSGM54       | 97977<br>04/04/97<br>209082<br>05/29/97 | pBluescript | 236             | 1133          | 316                 | 1069                |                      | 423                             | 474             | 1                   | 12                 | 13                           | 84             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 109      | HTSHE40       | 97977<br>04/04/97<br>209082<br>05/29/97  | pBluescript   | 119             | 1101          | 118                 | 956                 | 218                  | 218                             | 357             | 1                   | 31                 | 32                           | 89             |
| 110      | HTWAF58       | 97977<br>04/04/97<br>209082<br>05/29/97  | Lambda ZAP II | 120             | 282           | 1                   | 282                 | 137                  | 137                             | 358             | 1                   | 25                 | 26                           | 48             |
| 111      | HTWBY29       | 97977<br>04/04/97<br>209082<br>05/29/97  | pSport1       | 121             | 2635          | 1593                | 2489                | 1654                 | 1654                            | 359             | 1                   | 25                 | 26                           | 55             |
| 112      | HUKFC71       | 209007<br>04/28/97<br>209083<br>05/29/97 | Lambda ZAP II | 122             | 994           | 1                   | 932                 | 272                  | 272                             | 360             | 1                   | 15                 | 16                           | 221            |
| 113      | HCE3Q10       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 123             | 1542          | 1                   | 1542                | 143                  | 143                             | 361             | 1                   | 25                 | 26                           | 63             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 114      | HCEVR60       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 124             | 1390          | 82                  | 1390                | 127                  | 127                             | 362             | 1                   | 32                 | 33                           | 153            |
| 115      | HDTAW95       | 209007<br>04/28/97<br>209083<br>05/29/97 | pCMVSPORT 2.0 | 125             | 1288          | 412                 | 1288                | 571                  | 571                             | 363             | 1                   |                    |                              | 16             |
| 116      | HE6EL90       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 126             | 1517          | 1                   | 1452                | 243                  | 243                             | 364             | 1                   |                    |                              | 9              |
| 117      | HELB29        | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 127             | 1073          | 198                 | 1073                |                      | 776                             | 365             | 1                   |                    |                              | 13             |
| 118      | HERAH36       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 128             | 300           | 155                 | 300                 | 202                  | 202                             | 366             | 1                   |                    |                              | 17             |



| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 119      | HFXBW82       | 209007<br>04/28/97<br>209083<br>05/29/97 | Lambda ZAP II | 129             | 1275          | 1                   | 1275                | 56                   | 56                              | 367             | 1                   | 23                 | 24                           | 61             |
| 120      | HHPTD20       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 130             | 472           | 51                  | 472                 |                      | 243                             | 368             | 1                   |                    |                              | 32             |
| 121      | HIBED17       | 209007<br>04/28/97<br>209083<br>05/29/97 | Other         | 131             | 1950          | 284                 | 1927                | 395                  | 395                             | 369             | 1                   | 72                 | 73                           | 245            |
| 122      | HLTER03       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 132             | 990           | 1                   | 990                 | 78                   | 78                              | 370             | 1                   | 22                 | 23                           | 34             |
| 123      | HOABL56       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 133             | 1720          | 565                 | 1720                | 660                  | 660                             | 371             | 1                   | 18                 | 19                           | 21             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 124      | HPMCJ92       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 134             | 705           | 28                  | 705                 | 106                  | 106                             | 372             | 1                   | 28                 | 29                           | 98             |
| 125      | HPWAZ95       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 135             | 323           | 1                   | 323                 | 88                   | 88                              | 373             | 1                   | 27                 | 28                           | 78             |
| 126      | HRGBR18       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 136             | 582           | 1                   | 582                 |                      | 16                              | 374             | 1                   | 17                 | 18                           | 30             |
| 127      | HSUBW09       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 137             | 1021          | 1                   | 1021                | 153                  | 153                             | 375             | 1                   | 32                 | 33                           | 56             |
| 128      | HUKCO64       | 209007<br>04/28/97<br>209083<br>05/29/97 | Lambda ZAP II | 138             | 1777          | 1                   | 1339                | 198                  | 198                             | 376             | 1                   | 23                 | 24                           | 63             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector     | NT SEQ ID NO: X | NT Total Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|------------|-----------------|---------------|---------------------|---------------------|----------------------|------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 129      | H6EAA53       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 139             | 643           | 303                 | 643                 | 306                  | 306                          | 377             | 1                   | 14                 | 15                           | 38             |
| 130      | HAGAI11       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 140             | 1220          | 1                   | 1220                | 567                  | 567                          | 378             | 1                   | 50                 | 51                           | 98             |
| 131      | HAGAO39       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 141             | 721           | 1                   | 721                 |                      | 415                          | 379             | 1                   |                    |                              | 14             |
| 132      | HALSK07       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 142             | 1468          | 125                 | 1468                | 210                  | 210                          | 380             | 1                   | 29                 | 30                           | 33             |
| 133      | HALSQ59       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 143             | 300           | 4                   | 300                 | 101                  | 101                          | 381             | 1                   | 22                 | 23                           | 66             |
| 134      | HAIBP89       | 209877<br>05/18/98                       | Uni-ZAP XR | 144             | 2243          | 173                 | 2243                | 311                  | 311                          | 382             | 1                   | 27                 | 28                           | 317            |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 134      | HBGCB91       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR    | 237             | 1025          | 409                 | 1025                | 624                  | 624                             | 475             | 1                   | 20                 | 21                           | 25             |
| 135      | HBMTD81       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR    | 145             | 1082          | 163                 | 1082                | 357                  | 357                             | 383             | 1                   |                    |                              | 30             |
| 136      | HBXGK12       | 209008<br>04/28/97<br>209084<br>05/29/97 | ZAP Express   | 146             | 4313          | 1153                | 4313                | 1313                 | 1313                            | 384             | 1                   | 18                 | 19                           | 42             |
| 137      | HFKEJ07       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR    | 147             | 1183          | 1                   | 1183                | 149                  | 149                             | 385             | 1                   | 41                 | 42                           | 254            |
| 138      | HCQAI40       | 209008<br>04/28/97<br>209084<br>05/29/97 | Lambda ZAP II | 148             | 734           | 1                   | 734                 | 285                  | 285                             | 386             | 1                   |                    |                              | 19             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector      | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 139      | HCWHZ24       | 209008<br>04/28/97<br>209084<br>05/29/97 | ZAP Express | 149             | 1405          | 1                   | 1405                | 108                  | 108                             | 387             | 1                   | 34                 | 35                           | 63             |
| 140      | HE2GT20       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR  | 150             | 2890          | 1178                | 2890                | 1178                 | 1178                            | 388             | 1                   | 31                 | 32                           | 39             |
| 141      | HE8EY43       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR  | 151             | 2399          | 1181                | 2399                | 1265                 | 1265                            | 389             | 1                   | 30                 | 31                           | 34             |
| 142      | HFCEB37       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR  | 152             | 802           | 352                 | 802                 | 487                  | 487                             | 390             | 1                   |                    |                              | 10             |
| 143      | HFTCT67       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR  | 153             | 461           | 24                  | 461                 | 145                  | 145                             | 391             | 1                   | 37                 | 38                           | 63             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector          | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Peptide | AA SEQ ID NO: Y | First AA of Signal Peptide | Last AA of Signal Peptide | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|-----------------|-----------------|---------------|---------------------|---------------------|----------------------|-------------------------------------|-----------------|----------------------------|---------------------------|------------------------------|----------------|
| 144      | HGLAM46       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR      | 154             | 2388          | 818                 | 2388                | 648                  | 648                                 | 392             | 1                          |                           |                              | 18             |
| 145      | HHGBR15       | 209008<br>04/28/97<br>209084<br>05/29/97 | Lambda ZAP II   | 155             | 642           | 322                 | 642                 | 369                  | 369                                 | 393             | 1                          | 41                        | 42                           | 43             |
| 146      | HJAAU36       | 209008<br>04/28/97<br>209084<br>05/29/97 | pBluescript SK- | 156             | 1251          | 583                 | 1251                |                      | 933                                 | 394             | 1                          | 16                        | 17                           | 16             |
| 147      | HUSIT49       | 209008<br>04/28/97<br>209084<br>05/29/97 | pSport1         | 157             | 2127          | 247                 | 2127                | 383                  | 383                                 | 395             | 1                          | 47                        | 48                           | 83             |
| 148      | HKLAB16       | 209008<br>04/28/97<br>209084<br>05/29/97 | Lambda ZAP II   | 158             | 1625          | 817                 | 1625                | 1012                 | 1012                                | 396             | 1                          | 18                        | 19                           | 20             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector        | NT SEQ ID NO: X | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------------|---------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 149      | HILMMU76      | 209008<br>04/28/97<br>209084<br>05/29/97 | Lambda ZAP II | 159             | 1687                | 1307                | 1296                            | 397             | 1                   | 28                 | 29                           | 28             |
| 150      | HMSKQ35       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR    | 160             | 1842                | 172                 | 319                             | 398             | 1                   | 30                 | 31                           | 33             |
| 151      | HNHED86       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR    | 161             | 770                 | 1                   | 30                              | 399             | 1                   | 31                 | 32                           | 46             |
| 152      | HNHEJ88       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR    | 162             | 519                 | 1                   | 242                             | 400             | 1                   | 17                 | 18                           | 24             |
| 153      | HNHFQ63       | 209008<br>04/28/97<br>209084<br>05/29/97 | Uni-ZAP XR    | 163             | 753                 | 1                   | 164                             | 401             | 1                   | 17                 | 18                           | 67             |
| 154      | HOECU83       | 209009<br>04/28/97                       | Uni-ZAP XR    | 164             | 1893                | 1                   | 1637                            | 402             | 1                   | 28                 | 29                           | 85             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date | Vector      | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|-----------------------------|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 154      | HOECU83       | 209009<br>04/28/97          | Uni-ZAP XR  | 238             | 1400          | 189                 | 1400                |                      | 508                             | 476             | 1                   | 22                 | 23                           | 33             |
| 155      | HPTRC15       | 209009<br>04/28/97          | pBluescript | 165             | 2153          | 594                 | 2153                | 57                   | 57                              | 403             | 1                   | 26                 | 27                           | 82             |
| 156      | HSKCP69       | 209009<br>04/28/97          | Uni-ZAP XR  | 166             | 1251          | 219                 | 1120                | 49                   | 49                              | 404             | 1                   | 27                 | 28                           | 286            |
| 156      | HSKCP69       | 209009<br>04/28/97          | Uni-ZAP XR  | 239             | 1250          | 223                 | 1250                | 393                  | 393                             | 477             | 1                   | 32                 | 33                           | 171            |
| 157      | H6EAE26       | 209009<br>04/28/97          | Uni-ZAP XR  | 167             | 882           | 48                  | 882                 | 155                  | 155                             | 405             | 1                   | 33                 | 34                           | 153            |
| 158      | HAGBX03       | 209009<br>04/28/97          | Uni-ZAP XR  | 168             | 1208          | 1                   | 1208                | 290                  | 290                             | 406             | 1                   | 20                 | 21                           | 37             |
| 159      | HAGDQ47       | 209009<br>04/28/97          | Uni-ZAP XR  | 169             | 1258          | 1                   | 1258                | 44                   | 44                              | 407             | 1                   | 22                 | 23                           | 60             |
| 159      | HAGDQ47       | 209009<br>04/28/97          | Uni-ZAP XR  | 240             | 1307          | 1                   | 1307                | 44                   | 44                              | 478             | 1                   | 22                 | 23                           | 60             |
| 160      | HAICP19       | 209009<br>04/28/97          | Uni-ZAP XR  | 170             | 1624          | 89                  | 1483                | 128                  | 128                             | 408             | 1                   | 18                 | 19                           | 446            |
| 161      | HAUAE83       | 209009<br>04/28/97          | Uni-ZAP XR  | 171             | 2003          | 889                 | 2003                | 957                  | 957                             | 409             | 1                   | 29                 | 30                           | 64             |
| 162      | HBHAD12       | 209009<br>04/28/97          | Uni-ZAP XR  | 172             | 786           | 1                   | 786                 |                      | 176                             | 410             | 1                   | 17                 | 18                           | 23             |



| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 163      | HBMTY28       | 209009<br>04/28/97                       | Uni-ZAP XR | 173             | 1758          | 962                 | 1758                | 1184                 | 1184                            | 411             | 1                   | 27                 | 28                           | 34             |
| 164      | HBMPVP04      | 209009<br>04/28/97                       | Uni-ZAP XR | 174             | 1369          | 29                  | 557                 | 947                  | 947                             | 412             | 1                   | 33                 | 34                           | 41             |
| 164      | HBMPVP04      | 209009<br>04/28/97                       | Uni-ZAP XR | 241             | 888           | 330                 | 862                 |                      | 546                             | 479             | 1                   |                    |                              | 2              |
| 165      | HCDDDB78      | 209009<br>04/28/97                       | Uni-ZAP XR | 175             | 2379          | 750                 | 2379                | 901                  | 901                             | 413             | 1                   | 18                 | 19                           | 24             |
| 166      | HCEQA68       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 176             | 1348          | 1                   | 1348                | 12                   | 12                              | 414             | 1                   | 28                 | 29                           | 78             |
| 167      | HCEZS40       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 177             | 1502          | 178                 | 1502                | 388                  | 388                             | 415             | 1                   | 31                 | 32                           | 51             |
| 168      | HCFNF11       | 209010<br>04/28/97<br>209085<br>05/29/97 | pSport1    | 178             | 1637          | 26                  | 1607                | 152                  | 152                             | 416             | 1                   | 44                 | 45                           | 257            |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector      | NT SEQ ID NO: X | NT Total Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|-------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 169      | HCRBL20       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR  | 179             | 2911          | 1103                | 2858                | 192                  | 192                             | 417             | 1                   | 32                 | 33                           | 424            |
| 169      | HCRBL20       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR  | 242             | 1811          | 20                  | 1811                | 93                   | 93                              | 480             | 1                   | 36                 | 37                           | 95             |
| 170      | HCUBL62       | 209010<br>04/28/97<br>209085<br>05/29/97 | ZAP Express | 180             | 519           | 1                   | 519                 | 57                   | 57                              | 418             | 1                   | 28                 | 29                           | 32             |
| 171      | HDSAP81       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR  | 181             | 968           | 320                 | 968                 | 476                  | 476                             | 419             | 1                   | 27                 | 28                           | 79             |
| 172      | HE2CT29       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR  | 182             | 1128          | 1                   | 1128                | 111                  | 111                             | 420             | 1                   | 26                 | 27                           | 94             |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 173      | HE8MG65       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 183             | 2276 48       | 2276 88             |                     |                      | 88                              | 421             | 1                   | 37                 | 38                           | 257            |
| 173      | HE8MG65       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 243             | 2271 56       | 2232 79             |                     |                      | 79                              | 481             | 1                   | 43                 | 44                           | 170            |
| 174      | HE9FB42       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 184             | 3374 86       | 1705 277            |                     |                      | 277                             | 422             | 1                   | 40                 | 41                           | 704            |
| 174      | HE9FB42       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 244             | 2500 76       | 1693 518            |                     |                      | 518                             | 482             | 1                   | 1                  | 2                            | 623            |
| 175      | HEMAM41       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 185             | 1337 60       | 1328 175            |                     |                      | 175                             | 423             | 1                   | 39                 | 40                           | 190            |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date              | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal | NT Y | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|------------|-----------------|---------------|---------------------|---------------------|----------------------|-----------------------------|------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 175      | HEMAM41       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 245             | 1338          | 33                  | 1327                | 175                  | 175                         | 483  | 1               | 32                  | 33                 | 91                           |                |
| 176      | HEMCV19       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 186             | 941           | 33                  | 931                 | 79                   | 79                          | 424  | 1               | 23                  | 24                 | 178                          |                |
| 177      | HEMDX17       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 187             | 678           | 1                   | 678                 | 131                  | 131                         | 425  | 1               | 21                  | 22                 | 40                           |                |
| 177      | HEMDX17       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 246             | 654           | 1                   | 654                 | 137                  | 137                         | 484  | 1               |                     |                    | 12                           |                |
| 178      | HETAR54       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR | 188             | 1848          | 454                 | 1848                | 948                  | 948                         | 426  | 1               | 14                  | 15                 | 232                          |                |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 179      | HETBX14       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR    | 189             | 1292          | 303                 | 1292                | 207                  | 207                             | 427             | 1                   | 18                 | 19                           | 250            |
| 179      | HETBX14       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR    | 247             | 1146          | 157                 | 1146                | 74                   | 74                              | 485             | 1                   | 14                 | 15                           | 53             |
| 180      | HFGAB48       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR    | 190             | 906           | 156                 | 906                 | 628                  | 628                             | 428             | 1                   | 23                 | 24                           | 58             |
| 181      | HFKFI40       | 209010<br>04/28/97<br>209085<br>05/29/97 | Uni-ZAP XR    | 191             | 1941          | 120                 | 1002                | 213                  | 213                             | 429             | 1                   | 18                 | 19                           | 218            |
| 182      | HFXHN68       | 209010<br>04/28/97<br>209085<br>05/29/97 | Lambda ZAP II | 192             | 2118          | 777                 | 2118                | 966                  | 966                             | 430             | 1                   | 23                 | 24                           | 50             |
| 183      | HGBFO79       | 209011<br>04/28/97                       | Uni-ZAP XR    | 193             | 1538          | 259                 | 1538                | 273                  | 273                             | 431             | 1                   | 23                 | 24                           | 49             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date | Vector          | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|----------------------------|-----------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 184      | HGLAM56       | 209011<br>04/28/97         | Uni-ZAP XR      | 194             | 1098          | 68                  | 1098                |                      | 185                             | 432             | 1                   | 28                 | 29                           | 69             |
| 185      | HHLBA89       | 209011<br>04/28/97         | pBluescript SK- | 195             | 1001          | 1                   | 1001                | 324                  | 324                             | 433             | 1                   | 25                 | 26                           | 39             |
| 186      | HHPDW05       | 209011<br>04/28/97         | Uni-ZAP XR      | 196             | 1458          | 1                   | 1458                | 254                  | 254                             | 434             | 1                   | 17                 | 18                           | 104            |
| 186      | HHPDW05       | 209011<br>04/28/97         | Uni-ZAP XR      | 248             | 1443          | 1                   | 1443                | 246                  | 246                             | 486             | 1                   | 21                 | 22                           | 21             |
| 187      | HHPD37        | 209011<br>04/28/97         | pBluescript     | 197             | 1282          | 66                  | 1282                | 171                  | 171                             | 435             | 1                   | 19                 | 20                           | 37             |
| 188      | HHPDF70       | 209011<br>04/28/97         | pBluescript     | 198             | 951           | 26                  | 951                 |                      | 162                             | 436             | 1                   | 16                 | 17                           | 34             |
| 189      | HHSK25        | 209011<br>04/28/97         | Uni-ZAP XR      | 199             | 1740          | 1390                | 1740                | 1534                 | 1534                            | 437             | 1                   | 19                 | 20                           | 31             |
| 190      | HIASB53       | 209011<br>04/28/97         | pBluescript     | 200             | 1707          | 401                 | 1195                | 652                  | 652                             | 438             | 1                   | 26                 | 27                           | 126            |
| 191      | HJABZ65       | 209011<br>04/28/97         | pBluescript SK- | 201             | 779           | 1                   | 779                 | 23                   | 23                              | 439             | 1                   | 26                 | 27                           | 68             |
| 192      | HJPBB39       | 209011<br>04/28/97         | Uni-ZAP XR      | 202             | 1617          | 188                 | 1605                | 182                  | 182                             | 440             | 1                   | 28                 | 29                           | 91             |
| 193      | HHLK94        | 209011<br>04/28/97         | pBluescript     | 203             | 1974          | 1                   | 1794                | 112                  | 112                             | 441             | 1                   | 26                 | 27                           | 379            |

| Gene No. | cDNA Clone ID | ATCC Deposit No.:Z and Date | Vector        | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|-----------------------------|---------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 194      | HLHTC70       | 209011<br>04/28/97          | pBluescript   | 204             | 1057          | 229                 | 1057                | 365                  | 365                             | 442             | 1                   | 23                 | 24                           | 22             |
| 195      | HLMIW92       | 209011<br>04/28/97          | Lambda ZAP II | 205             | 721           | 1                   | 721                 | 244                  | 244                             | 443             | 1                   | 25                 | 26                           | 46             |
| 196      | HLTCY93       | 209011<br>04/28/97          | Uni-ZAP XR    | 206             | 2465          | 988                 | 2465                | 387                  | 387                             | 444             | 1                   | 27                 | 28                           | 214            |
| 197      | HLTDB65       | 209011<br>04/28/97          | Uni-ZAP XR    | 207             | 1480          | 1                   | 1480                |                      | 371                             | 445             | 1                   | 15                 | 16                           | 143            |
| 198      | HMSHM43       | 209011<br>04/28/97          | Uni-ZAP XR    | 208             | 872           | 1                   | 872                 | 35                   | 35                              | 446             | 1                   | 18                 | 19                           | 36             |
| 199      | HMSHQ24       | 209011<br>04/28/97          | Uni-ZAP XR    | 209             | 1779          | 16                  | 1779                | 148                  | 148                             | 447             | 1                   | 24                 | 25                           | 36             |
| 200      | HNFAH08       | 209011<br>04/28/97          | Uni-ZAP XR    | 210             | 2110          | 592                 | 2110                | 611                  | 611                             | 448             | 1                   | 18                 | 19                           | 191            |
| 201      | HNGAO10       | 209011<br>04/28/97          | Uni-ZAP XR    | 211             | 938           | 1                   | 938                 | 107                  | 107                             | 449             | 1                   | 27                 | 28                           | 30             |
| 202      | HNGBE45       | 209011<br>04/28/97          | Uni-ZAP XR    | 212             | 1551          | 1                   | 1551                | 114                  | 114                             | 450             | 1                   | 21                 | 22                           | 100            |
| 203      | HNHAZ16       | 209011<br>04/28/97          | Uni-ZAP XR    | 213             | 997           | 1                   | 997                 | 202                  | 202                             | 451             | 1                   | 24                 | 25                           | 36             |
| 204      | HNHCM59       | 209011<br>04/28/97          | Uni-ZAP XR    | 214             | 1496          | 1                   | 1132                |                      | 165                             | 452             | 1                   | 28                 | 29                           | 41             |

| Gene No. | cDNA Clone ID | ATCC Deposit No:Z and Date               | Vector     | NT SEQ ID NO: X | Total NT Seq. | 5' NT of Clone Seq. | 3' NT of Clone Seq. | 5' NT of Start Codon | 5' NT of First AA of Signal Pep | AA SEQ ID NO: Y | First AA of Sig Pep | Last AA of Sig Pep | First AA of Secreted Portion | Last AA of ORF |
|----------|---------------|--|------------|-----------------|---------------|---------------------|---------------------|----------------------|---------------------------------|-----------------|---------------------|--------------------|------------------------------|----------------|
| 205      | HOSFM22       | 97977<br>04/04/97<br>209082<br>05/29/97  | Uni-ZAP XR | 215             | 1308          | 501                 | 1308                | 1081                 | 1081                            | 453             | 1                   | 46                 | 47                           | 48             |
| 206      | HPHAC88       | 97977<br>04/04/97<br>209082<br>05/29/97  | Uni-ZAP XR | 216             | 1705          | 384                 | 1705                | 549                  | 549                             | 454             | 1                   | 23                 | 24                           | 24             |
| 207      | HCDEO95       | 209007<br>04/28/97<br>209083<br>05/29/97 | Uni-ZAP XR | 217             | 999           | 608                 | 999                 | 273                  | 273                             | 455             | 1                   | 22                 | 23                           | 54             |



Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related  
5 DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits  
10 contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq."  
15 and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is  
20 identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal  
25 peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

30 SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently

accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also

5 hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1.

10 Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the

15 actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the

20 generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods.

25 The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

30 The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed

herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or a deposited clone, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the secreted protein.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or a cDNA contained in ATCC deposit Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide encoded by the cDNA contained in ATCC deposit Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide sequence encoded by the cDNA contained in ATCC deposit Z are also encompassed by the invention.

#### 10        Signal Sequences

The present invention also encompasses mature forms of the polypeptide having the polypeptide sequence of SEQ ID NO:Y and/or the polypeptide sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of

predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

5           In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis  
10 of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

          As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence  
15 shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present  
20 invention.

          Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of  
25 directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as described below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present  
30 invention.

### **Polynucleotide and Polypeptide Variants**

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X, the complementary strand thereto, and/or the cDNA sequence contained in a deposited clone.

- 5       The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y and/or encoded by a deposited clone.

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many  
10       regions, identical to the polynucleotide or polypeptide of the present invention.

- The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the  
15       nucleotide coding sequence contained in a deposited cDNA clone or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited clone, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein).
- 20       Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

- The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%,  
25       95%, 96%, 97%, 98%, 99% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, the polypeptide sequence encoded by the cDNA contained in a deposited clone, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein).

- By a nucleic acid having a nucleotide sequence at least, for example, 95%  
30       "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each

100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then

subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference



sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, an amino acid sequences shown in Table 1 (SEQ ID NO:Y) or to the amino acid sequence encoded by cDNA contained in a deposited clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal

residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not  
5 show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be  
10 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal  
15 ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing  
20 alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced  
25 for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an  
30 organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are

included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make  
5 phenotypically silent amino acid substitutions is provided in Bowie et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in  
10 different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the  
15 protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.  
20 (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the  
25 protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic  
30 residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a  
5 substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification or (v) fusion of the polypeptide with  
10 another compound, such as albumin (including, but not limited to, recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

15 For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340  
20 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50  
25 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of the  
30 present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or

fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

5        **Polynucleotide and Polypeptide Fragments**

The present invention is also directed to polynucleotide fragments of the polynucleotides of the invention.

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence which: is a portion of that contained in  
10 a deposited clone, or encoding the polypeptide encoded by the cDNA in a deposited clone; is a portion of that shown in SEQ ID NO:X or the complementary strand thereto, or is a portion of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:Y. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt,  
15 and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in a deposited clone or the nucleotide sequence shown in SEQ ID NO:X. In this context "about" includes the particularly recited value, a value larger  
20 or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the  
25 invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500,  
30 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this

context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed

5 herein. Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y or encoded by the  
10 cDNA contained in a deposited clone. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40,  
15 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.  
20 Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-  
25 60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also  
30 preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

- 5 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotides encoding these domains are also contemplated.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily  
10 identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Preferably, the polynucleotide fragments of the invention encode a  
15 polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) polypeptide of invention protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a  
20 polypeptide of the invention for binding) to an antibody to the polypeptide of the invention], immunogenicity (ability to generate antibody which binds to a polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of polypeptides of the invention, and fragments,  
25 variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the invention for binding to an antibody of the polypeptide of the invention, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using  
30 techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using



colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

10 In another embodiment, where a ligand for a polypeptide of the invention identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See 15 generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates of binding of a polypeptide of the invention to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the 20 invention and fragments, variants derivatives and analogs thereof to elicit related biological activity related to that of the polypeptide of the invention (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

## 25 **Epitopes and Antibodies**

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. Z or encoded by a polynucleotide that 30 hybridizes to the complement of the sequence of SEQ ID NO:X or contained in ATCC deposit No. Z under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses

polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize  
5 to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention  
10 encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA  
15 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not  
20 necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

In the present invention, antigenic epitopes preferably contain a sequence of at  
25 least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100  
30 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies,

that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an

immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may  
5 be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or  
10 antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example,  
15 polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)).  
20 In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the  
25 present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be  
30 fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opinion Biotechnol.* 8:724-33

(1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

### Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin

molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be

excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included.

Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the



epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes  
5 antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand  
10 binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described  
15 supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent  
20 ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but  
25 do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists  
30 for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No.

- 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).
- 10       Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g.,
- 15       Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of

numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

5           The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal  
10   antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and  
15   potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be  
20   produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not  
25   limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma  
30   technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an

immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are  
5 selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating  
10 monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody  
15 able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments).  
20 F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which  
25 carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid  
30 surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage

gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic  
5 et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225;  
10 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and  
15 expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-  
20 34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999  
25 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal  
30 antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol.

Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into

mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.

10 Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

25

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

30

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using

techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be  
5 used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to  
10 bind its ligands/receptors, and thereby block its biological activity.

#### *Polynucleotides Encoding Antibodies*

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The  
15 invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

20 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the  
25 synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a  
30 particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library



generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe  
5 specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the  
10 antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor,  
15 NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light  
20 chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted  
25 within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of  
30 the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino

acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other  
5 alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes  
10 from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized  
15 antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain  
20 antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

#### 25 *Methods of Producing Antibodies*

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment,  
30 derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a

polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as

bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems  
5 infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO,  
10 BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole  
15 recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2  
20 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which  
25 direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic  
30 Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such

fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the  
5 GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus  
10 and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation  
15 control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad.  
20 Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and  
25 initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression  
30 of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein.

Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt,

which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 5 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. 10 (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

15       The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in 20 culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

      The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second 25 vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic 30 free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for  
5 the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

10 The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through  
15 linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention  
20 to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS  
25 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may  
30 be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any



combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to

identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred  
5   embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags  
10   useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used  
15   diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent  
20   materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No.  
25   4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone,  
30   fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin,

and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"),

granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports  
5 include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld  
10 et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results,  
15 And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

20 Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can  
25 be used as a therapeutic.

### *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present  
30 invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific

epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with  
5 antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to  
10 prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

#### *Assays For Antibody Binding*

15 The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions,  
20 gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by  
25 reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1%  
30 Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A

and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes

the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the

5 coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

10 The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the

15 antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of

20 increasing amounts of an unlabeled second antibody.

#### *Therapeutic Uses*

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal,

25 and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic

30 antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any

one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or  
5 conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the  
10 antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

15 The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

20 The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment,  
25 human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and  
30 therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention,



including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

### *Gene Therapy*

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other

desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific  
5   embodiments, the expressed antibody molecule is a single chain antibody;  
alternatively, the nucleic acid sequences include sequences encoding both the heavy  
and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or  
10   indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be  
15   accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun;  
20   Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target  
25   cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT  
30   Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination

(Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

10 In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, 15 e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. 20 The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or 25 progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy 30 encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages,

neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

5 In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or  
10 progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

15 In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

#### 20 *Demonstration of Therapeutic or Prophylactic Activity*

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition  
25 include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a  
30 specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

*Therapeutic/Prophylactic Administration and Composition*

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment;

this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when  
5 administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)  
10

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose  
20 (see, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138 (1984)).  
25

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote  
30 expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by

use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g.,  
5 Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a  
10 pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic  
15 is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid  
20 carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering  
25 agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium  
30 saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of



the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with  
5 routine procedures as a pharmaceutical composition adapted for intravenous  
administration to human beings. Typically, compositions for intravenous  
administration are solutions in sterile isotonic aqueous buffer. Where necessary, the  
composition may also include a solubilizing agent and a local anesthetic such as  
lignocaine to ease pain at the site of the injection. Generally, the ingredients are  
10 supplied either separately or mixed together in unit dosage form, for example, as a dry  
lyophilized powder or water free concentrate in a hermetically sealed container such  
as an ampoule or sachette indicating the quantity of active agent. Where the  
composition is to be administered by infusion, it can be dispensed with an infusion  
bottle containing sterile pharmaceutical grade water or saline. Where the composition  
15 is administered by injection, an ampoule of sterile water for injection or saline can be  
provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms.  
Pharmaceutically acceptable salts include those formed with anions such as those  
derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those  
20 formed with cations such as those derived from sodium, potassium, ammonium,  
calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol,  
histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the  
treatment, inhibition and prevention of a disease or disorder associated with aberrant  
25 expression and/or activity of a polypeptide of the invention can be determined by  
standard clinical techniques. In addition, in vitro assays may optionally be employed  
to help identify optimal dosage ranges. The precise dose to be employed in the  
formulation will also depend on the route of administration, and the seriousness of the  
disease or disorder, and should be decided according to the judgment of the  
30 practitioner and each patient's circumstances. Effective doses may be extrapolated  
from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human  
5 antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by  
10 modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture,  
15 use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### *Diagnosis and Imaging*

Labeled antibodies, and derivatives and analogs thereof, which specifically  
20 bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body  
25 fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder,  
30 comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level,

whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods

including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce  
5 diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of  
10 Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the  
15 labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by  
20 repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label  
25 used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

30 In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with

a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is  
5 detected in a patient using magnetic resonance imaging (MRI).

### *Kits*

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified  
10 antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present  
15 invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

20 In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically  
25 immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide  
30 antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may

also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in  
5 screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be  
10 a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present  
15 invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the  
20 reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip  
25 sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated  
30 antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound

recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

### **Fusion Proteins**

5 Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target  
10 cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur  
15 through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell  
20 or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and  
25 specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins  
30 consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).)

Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).) Polynucleotides comprising or alternatively consisting of  
5 nucleic acids which encode these fusion proteins are also encompassed by the invention.

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a  
10 fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for  
15 example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker  
20 sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for  
25 instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides  
30 or the polypeptides of the present invention.



### Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral  
5 vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate,  
10 such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac  
15 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a  
20 translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin  
25 resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as  
30 CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated

or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express the polypeptide of the present invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., et al., *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., et al., *Yeast* 5:167-77 (1989); Tschopp, J.F., et al., *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a protein of the invention by virtue of the strong *AOX1*

promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, 5 pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding 10 sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs 15 discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and 20 which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination, resulting in the formation of a new transcription unit (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; U.S. Patent No. 25 5,733,761, issued March 31, 1998; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

30 In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and

Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide sequence of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid  
5 analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid,  $\gamma$ -Abu,  $\epsilon$ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine,  
10 norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, fluoro-amino acids, designer amino acids such as  $\beta$ -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

15 The invention encompasses polypeptides which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, *etc.* Any of numerous chemical modifications may be carried out by known techniques, including but not  
20 limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; *etc.*

Additional post-translational modifications encompassed by the invention include, for example, *e.g.*, N-linked or O-linked carbohydrate chains, processing of  
25 N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and  
30 isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as

increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent NO: 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG

to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated  
5 polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for  
10 therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid,  
15 glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

20 One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be  
25 performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be  
30 accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions,

substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.



The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The polypeptides of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, *Therapeutics*) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these polypeptides as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (*e.g.*, containing polypeptides having identical or different amino acid sequences) or a homotrimer (*e.g.*, containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (*i.e.*, polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional  
5   embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as,  
10   for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion  
15   protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence ( *e.g.*, that recited in the sequence listing, or contained in the polypeptide encoded by a deposited clone). In one  
20   instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (*i.e.*, naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the  
25   heterologous polypeptide sequence in a fusion protein of the invention.

In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, *e.g.*, US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in an Fc fusion protein of the invention (as  
30   described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for

example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous

polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers  
5 of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues  
10 located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers  
15 containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its  
20 entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent  
25 Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse  
30 orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described

herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by  
5 reference in its entirety).

### Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes  
10 known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present  
15 invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of  
20 somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per  
25 day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries and computer mapping techniques (See, e.g., Shuler, Trends  
30 Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety)..

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see  
5 Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

10 The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g., Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-  
15 492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage  
20 analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated  
25 with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural  
30 alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide

and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected  
5 individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis  
10 of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

15 In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the present invention and a suitable container. In a specific  
20 embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the present invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder, has already been made according to  
25 conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the present invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotide of the present  
30 invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the present invention or the level of the mRNA encoding the polypeptide in a first biological sample either directly (e.g., by determining or

estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard  
5 being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

10 By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains the polypeptide of the present invention or mRNA. As indicated, biological samples include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and other tissue  
15 sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic  
20 method and/or kits in which polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the present invention attached may be used to identify polymorphisms between the polynucleotide sequences, with  
25 polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, including cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

30 The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the



preferred form if the polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention is useful for detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative diseases, disorders, and/or conditions are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al.,

"The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)).

Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by  
5 insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., supra) Indeed, the human counterparts of the oncogenes involved in  
10 some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International  
15 Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580;  
20 Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative diseases, disorders, and/or conditions of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit  
25 proliferative phenotypes.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca  
30 Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the

polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456  
5 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into  
10 polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat or prevent disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective  
15 gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute  
20 biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of  
25 "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions  
30 of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a

unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

30

#### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression  
5 in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known  
10 in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins  
15 can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as  
20 deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear  
25 magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5  
30 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics

of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which  
5 involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high  
10 amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the  
15 development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat, prevent, and/or diagnose disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different  
20 polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a  
25 desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat, prevent, and/or diagnose disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce  
30 overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover,  
5 the polypeptides of the present invention can be used to test the following biological activities.

#### Gene Therapy Methods

10 Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the  
15 invention that operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a  
20 polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the invention *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Beldegrun et al., J. Natl. Cancer Inst., 85:207-216 (1993); Ferrantini et al., Cancer Research, 53:107-1112 (1993); Ferrantini et al., J.  
25 Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato, et al., Human Gene Therapy 7:1-10 (1996); Santodonato, et al., Gene Therapy 4:1246-1255 (1997); and Zhang, et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are  
30 arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs of the invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of polynucleotide sequence of the invention. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotides of the invention.



Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked *nucleic acid* sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or

bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs of the invention are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA, 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA, 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem., 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA, 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication NO: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of

DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc. Natl. Acad. Sci. USA, 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

5        Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC),  
10        dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

      For example, commercially dioleoylphosphatidyl choline (DOPC),  
dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine  
15        (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2  
20        hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available  
25        to those of skill in the art.

      The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology, 101:512-527 (1983),  
30        which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated.

SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta*, 394:483 (1975); Wilson et al., *Cell*, 17:77 (1979)); ether injection (Deamer et al., *Biochim. Biophys. Acta*, 443:629 (1976); Ostro et al., *Biochem. Biophys. Res. Commun.*, 76:836 (1977); Fraley et al., *Proc. Natl. Acad. Sci. USA*, 76:3348 (1979)); detergent dialysis (Enoch et al., *Proc. Natl. Acad. Sci. USA*, 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.*, 255:10431 (1980); Szoka et al., *Proc. Natl. Acad. Sci. USA*, 75:145 (1978); Schaefer-Ridder et al., *Science*, 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent NO: 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding polypeptides of the invention. Retroviruses from which the retroviral plasmid vectors

may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

5       The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy, 1:5-14 (1990), which is incorporated herein by  
10 reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and  $\text{CaPO}_4$  precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

15       The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding polypeptides of the invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express polypeptides of the invention.

      In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with  
20 polynucleotides of the invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses polypeptides of the invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional  
25 mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al., Am. Rev. Respir. Dis., 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science, 252:431-434 (1991);  
30 Rosenfeld et al., Cell, 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al. Proc. Natl. Acad. Sci. USA, 76:6606 (1979)).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.*, 3:499-503 (1993); Rosenfeld et al., *Cell*, 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.*, 4:759-769 (1993); Yang et al., *Nature Genet.*, 7:362-369 (1994); Wilson et al.,  
5 *Nature*, 365:691-692 (1993); and U.S. Patent NO: 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express E1a and E1b, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other  
10 varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of  
15 infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*,  
20 using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, *Curr. Topics in Microbiol. Immunol.*, 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is  
25 limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell  
30 integration. The polynucleotide construct containing polynucleotides of the invention is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor

Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses.

- 5 Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct of the invention. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the desired gene product.

- 10 Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding the polypeptide sequence of interest) via homologous recombination (see, e.g., U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO  
15 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

- Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter.  
20 Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous  
25 polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

- The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same  
30 restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the

amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotides encoding polypeptides of the present invention may be administered along with other polynucleotides encoding other angiogenic proteins. Angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

Preferably, the polynucleotide encoding a polypeptide of the invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle



accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium

- 5 phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers. (Kaneda et al., Science, 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is  
10 administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a  
15 patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery  
20 vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be  
25 performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA, 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the  
30 gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a

polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian. Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly

#### **Biological Activities**

The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

Polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

#### **Immune Activity**

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis,

producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or  
5 infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to  
10 treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
15 present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked  
20 immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type),  
25 Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID),  
30 common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

5        Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare  
10 lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

15        In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or  
20 antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic  
25 alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented,  
30 diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary

inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific  
5 preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies,  
10 and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment IgA nephropathy is treated,  
15 prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides,  
20 antibodies, and/or agonists or antagonists of the present invention

In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
25 present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders,  
30 and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or

agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain



injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are  
5 characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory  
10 disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis,  
15 chondritis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis,  
20 peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose,  
25 prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or  
30 antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides,

antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

5        In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

10       Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an  
15       existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

20       In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

25       In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art.

30       In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In

another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat

infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
5 and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat,  
10 rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an  
15 immune response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
20 and/or agonists or antagonists of the present invention are used as an activator of T cells.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of  
25 immunosuppressive therapies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
30 and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants  
10 (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment,  
15 compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost  
20 immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists  
30 or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious

mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one  
5     embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to  
10    modulate the immune system.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

15     In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more  
20    rapidly their susceptibility profile would likely change.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

25     In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the  
30    pretreatment of bone marrow samples prior to transplant.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based

therapy for genetically inherited disorders resulting in immuno-  
incompetence/immunodeficiency such as observed among SCID patients.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a means of  
5 activating monocytes/macrophages to defend against parasitic diseases that effect  
monocytes such as Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a means of  
regulating secreted cytokines that are elicited by polypeptides of the invention.

10 In another embodiment, polypeptides, antibodies, polynucleotides and/or  
agonists or antagonists of the present invention are used in one or more of the  
applications described herein, as they may apply to veterinary medicine.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a means of  
15 blocking various aspects of immune responses to foreign agents or self. Examples of  
diseases or conditions in which blocking of certain aspects of immune responses may  
be desired include autoimmune disorders such as lupus, and arthritis, as well as  
immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and  
diseases/disorders associated with pathogens.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a therapy for  
preventing the B cell proliferation and Ig secretion associated with autoimmune  
diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus  
and multiple sclerosis.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a inhibitor of B  
and/or T cell migration in endothelial cells. This activity disrupts tissue architecture  
or cognate responses and is useful, for example in disrupting immune responses, and  
blocking sepsis.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides  
and/or agonists or antagonists of the present invention are used as a therapy for  
chronic hypergammaglobulinemia evident in such diseases as monoclonal

gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

10 The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized



by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne  
5 infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media,  
10 conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal  
15 dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a  
20 subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be  
25 prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed  
30 diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, 10 such as, for example, an individual who has undergone a partial or complete splenectomy.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the 15 invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

20 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of 25 producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of 30 monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention in an organ system listed above.

### **Blood-Related Disorders**

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing

5 hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes.

10 Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

15 In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the

20 polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with

25 mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass

30 machines).

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to

prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

5       The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes,  
10   lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
15   present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for  
20   example eosinophilia.

      The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

      Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may  
25   be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or  
30   antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious

anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadiazine. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thrombasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophilias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary

Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored  
5 using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in  
10 a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug  
15 treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or  
20 associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis  
25 may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer.

Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in  
30 diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or

antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in  
5 specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
10 present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment,  
15 anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

20 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies,  
25 and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists  
30 of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or

macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.



In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

5 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

10 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

15 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

20

#### **Hyperproliferative Disorders**

In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

30 For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune

response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue

- Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related
- 5 Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular
- 10 Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant
- 15 Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and
- 20 Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer,
- 25 Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma,
- 30 Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive

Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal  
5 Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or  
10 treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal  
15 growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated  
20 with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic  
25 hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia,  
30 senile sebaceous hyperplasia, and verrucous hyperplasia.

Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders

which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic  
5 ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

Dysplasia is frequently a forerunner of cancer, and is found mainly in the  
10 epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented,  
15 and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital  
20 ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws,  
25 familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial  
30 dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia,

pseudoachondroplastic spondyloepiphyseal dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphyseal dysplasia, and ventriculoradial dysplasia.

Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including  
5 polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

In another embodiment, a polypeptide of the invention, or polynucleotides,  
10 antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or  
15 agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein,  
20 may be used to treat acute myelogenous leukemia.

Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the  
25 inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer,  
30 intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and

ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma,

pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.



Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells.

10 In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably

15 an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other

20 polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the

25 present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the

30 destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By

"biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in  
5 tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described  
10 disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may  
15 be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of  
20 the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering  
25 a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or  
30 activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present

invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins

(See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

5 Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4  
10 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions  
15 containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic  
20 and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and  
25 immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

### **Renal Disorders**

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
30 present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented,

and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

5       Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, 10 membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal 15 glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting from urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, 20 nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, 25 nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, 30 analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE),

Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g.,

5 glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema,

10 hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous

15 injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more

20 detail below. Methods of delivering polynucleotides are described in more detail herein.

### **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present

25 invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral

30 arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia,

patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects,

- 5 Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac  
10 edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease,  
15 ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine  
20 Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia,  
25 Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia,  
30 tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular



stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include, but are not limited to, coronary disease, such as  
5 angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema,  
10 aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's  
15 disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include, but are not limited to, dissecting aneurysms, false  
20 aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery  
25 occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis,  
30 Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia

(including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

## **Respiratory Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's

- nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).
- Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia spp.*), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis,

desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial),  
5 bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

#### Anti-Angiogenesis Activity

10 The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastenejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound  
15 healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization  
20 including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J.*  
25 *Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

30 The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present

invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*,  
5 Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists  
10 may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder,  
15 thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and  
20 Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a  
25 catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These  
30 disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy,

retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

- 10 For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

- 15 Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

- 25 Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion,

but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly  
5 after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-  
10 3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or  
15 agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the  
20 compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

25 Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

30 Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or



agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the polynucleotides, polypeptides, agonists and/or antagonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochelie minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or antagonists may also be used in controlling menstruation or administered as either a

peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch  
5 granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal  
10 surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic  
15 compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-  
20 angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the  
25 site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly  
30 preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum

(VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

- 5           A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence  
10 of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem.  
15 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987);  
20 Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminimidazole; and metalloproteinase inhibitors such as BB94.

25           **Diseases at the Cellular Level**

- Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-  
30 dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,

lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma,

craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as  
5 agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's  
10 disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and  
15 liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

### **Wound Healing and Epithelial Cell Proliferation**

In accordance with yet a further aspect of the present invention, there is  
20 provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present  
25 invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing  
30 conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or

antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avascular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentopial graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat

10 gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or

15 antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect

20 the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to

25 various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke

30 inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as



agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins  
10 known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists  
15 of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

## 20 Neural Activity and Neurological Diseases

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides,  
25 and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the  
30 following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or

ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated

with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev.*

*Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or  
5 Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral  
10 ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or  
15 antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or  
20 detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency,  
25 pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as  
30 ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell

leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention  
5 include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's  
10 Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

15 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as  
20 multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis,  
25 encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-  
30 Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebral pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral  
5 toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

10 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as  
15 Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as  
20 Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include  
25 cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral  
30 leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis,

transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms  
5 such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis  
10 such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity,  
15 encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie  
20 Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing  
25 disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders  
30 such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman



syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases

such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention  
5 include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as  
10 polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

15

#### **Endocrine Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine  
20 system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine  
25 system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

30 Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with

pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include

5 disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the

10 pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (*Hashimoto's thyroiditis*, *subacute granulomatous*

15 thyroiditis, and *silent lymphocytic thyroiditis*), *Pendred's syndrome*, *myxedema*, *cretinism*, *thyrotoxicosis*, *thyroid hormone coupling defect*, *thymic aplasia*, *Hurthle cell tumours of the thyroid*, *thyroid cancer*, *thyroid carcinoma*, *Medullary thyroid carcinoma*; disorders and/or diseases of the parathyroid, such as, for example, *hyperparathyroidism*, *hypoparathyroidism*; disorders and/or diseases of the

20 hypothalamus.

In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat,

25 prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

30

In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to

diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or  
5 antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, and/or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and  
10 other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the  
15 "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's  
20 weight. In specific embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene  
25 and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including  
30 cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells,

cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example,  
5 polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders  
10 associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in the "FEATURES OF PROTEIN" section for each gene.

#### **Reproductive System Disorders**

15 The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and  
20 diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and  
25 orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm  
30 production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate  
5 neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica  
10 obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis,  
15 giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and  
20 impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or  
25 disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and  
30 gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of

diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example,

cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as  
5 early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio  
10 placenta, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral  
15 valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus erythematosus, rheumatoid arthritis, myasthenia  
20 gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal),  
25 breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis,  
30 mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and



agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

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### **Infectious Disease**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

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Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic

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fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific  
5   embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment  
10   polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-  
15   Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthracis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium difficile*,  
20   *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diphtheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia,  
25   Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae* and *Mycobacterium tuberculosis*), Vibrio (e.g., *Vibrio cholerae*), Neisseriaceae (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), Pasteurellaceae, Proteus, Pseudomonas  
30   (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningioccus, Pneumococcus and Streptococcus (e.g., *Streptococcus*

*pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., meningitis types A and B), chlamydia, syphilis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Schistosoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be

used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of

non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

#### Gastrointestinal Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile

hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, 5 hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic 10 porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and 15 glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, 20 acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous 25 adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases 30 (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis,

- amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal  
5 volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal  
10 lymphangiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia,  
15 gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and  
20 hemorrhagic colitis.

- Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract  
neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus,  
25 esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's  
30 diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome),



stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)),  
5 hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

### Chemotaxis

10 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then  
15 fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the  
20 number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as  
25 agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

### Binding Activity

30 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The

binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

5            Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable  
10 of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

            Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane  
15 containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

            The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving  
20 competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

            Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate  
25 compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

            Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The  
30 antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., *Current Protocols in Immun.*, 1(2), Chapter 5, (1991)). For example, expression cloning is employed  
5 wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are  
10 exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-  
15 transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and  
20 exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

25 Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721,  
30 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R.

*Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$  thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the

uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

5           In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following  
10 interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

15           All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from  
20 suitably manipulated cells or tissues.

          Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of  
25 identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

5 As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention  
10 (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate  
15 episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

20 By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes  
25 known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a  
30 non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of

benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxycetamide derivatives of doxorubicin.

5           **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected  
10 compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in  
15 such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation  
20 of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the  
25 present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a  
30 particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present

invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein.

Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### **Polypeptides of the Invention Binding Peptides and Other Molecules**

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of: contacting a polypeptide of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptide of the invention.

The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the



invention. The molecules having a selective affinity for the polypeptide of the invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alternatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction.

Such a wash step may be particularly desirable when the polypeptide of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide  
5 libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature*  
10 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al.,  
15 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157;  
20 Kay et al., 1993, *Gene* 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:9022-9026.

25 By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically  
30 transformed combinatorial library, is described by Ostresh et al. (1994, *Proc. Natl. Acad. Sci. USA* 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is

great. For example, Ecker and Crooke, 1995, *Bio/Technology* 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992; *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those

library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

5 In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the  
10 polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

15 Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine.

20 Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a polypeptide of the invention binding  
25 molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

30 The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

### Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited  
5 clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, *Neurochem.*, 56:560 (1991). *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988).

Antisense technology can be used to control gene expression through antisense DNA  
10 or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, *Neurochem.*, 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research*, 6:3073 (1979); Cooney et al., *Science*, 241:456 (1988); and Dervan et al., *Science*, 251:1300  
15 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These  
20 experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complementary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is  
25 heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA  
30 oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense

RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or  
5 a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard  
10 in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early  
15 promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

20 The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA,  
25 forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the  
30 invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' - non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, *e.g.*, Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are



commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of

the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

#### **Other Activities**

The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide

may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to

modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

#### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the  
5 nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

10 Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ  
15 ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule  
20 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization  
25 conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type  
30 Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the  
5 ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
10 sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human  
15 cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological  
20 sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained  
25 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences  
30 comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence

selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least

95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise  
5 a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1  
10 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the  
15 amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the  
20 Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid  
25 sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

30 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human



cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted  
5 protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the  
10 amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in  
15 the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein  
20 encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a  
25 sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table  
30 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a

sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained  
5 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

10 Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at  
15 least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

20 Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules  
25 in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in  
30 Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a  
5 sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a  
10 biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a  
15 complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
20 sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y  
25 wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide  
30 sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone  
5 identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of  
10 making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making  
15 an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and  
20 said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

25 Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

30 The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-

human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

- 5 In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 2, preferably excluded are one or more polynucleotides comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 2 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3
- 10 of Table 2. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences referred to in the fifth column of Table 2. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby
- 15 incorporated by reference in their entirety.

TABLE 2

| Gene No. | cDNA Clone ID | NT SEQ ID NO: X | Contig ID | Public Accession Numbers   |
|----------|---------------|-----------------|-----------|--|
| 1        | HLHDS67       | 11              | 396448    | T84556, R77553, H77877, H96723, N22894, N24112, N25474, N31281, N31410, N31809, N42470, N58904, N59834, N67726, W03552, W15430, W78090, W79576, W94783, W95299, AA112608, AA126875, AA127799, AA133859, AA169532, AA169601 |
| 2        | HLHDZ58       | 12              | 396869    | R44557, R44557, H15251, H16568   |
| 10       | HOUBE18       | 20              | 407070    | T97913, R21634, R47833, R49975, R54690, R55015, R55153, R62188, R64576, R80153, R80154, R81484, R81724, H13709, H13762, H49782, N33449, N34466, N42422, N42873, N50673, N53663, N73029, W44598, W73379, W73403, AA088385   |
| 11       | HOUDL69       | 21              | 396821    | T98572, T98573, T99692, R46104, R46177, R46104, R46177, R77699, R77698, R81185, R81291, R84758, R84835, N73056, W88438, W89202   |
| 12       | HPMFI71       | 22              | 407378    | R53416, R54007, H14084, H45951, H75270, H75382, N27106, N40516, W37083, W37084, W72173   |
| 15       | HPTBB03       | 25              | 399928    | T58022, T86930, R11711, T83207, T86107,  |

|    |         |     |        |  |
|----|---------|-----|--------|--|
|    |         |     |        | T96449, R17686, R36056, R36058, R49138, R49140, R53540, R53651, R49138, R73230, R76352, H06054, H13390, H14662, H17478, H17586, H24833, H29049, H29151, H92319, H92379, N24774, N32793, N42234, N94618, W15347, W31392, W31984, W39439, W95395, W95353, AA088664, AA088803, AA102451, AA130481, AA130482, AA143411, AA143667, AA146597, AA148224, AA148225, AA156280, AA156391, AA158602, AA158959, AA158958, AA158971, AA158970, AA164777 |
| 16 | HPTWA66 | 26  | 614220 | R32953, R48005, R52174, R53999, R94185, N58829, N75247, W86429, AA024852, AA024935, AA101581, AA101582, AA121348, AA121367, AA135194, AA135274, AA149607, AA149718, AA181794, AA461476, AA460122   |
| 16 | HPTWA66 | 219 | 408041 | T56759, T63654, R48005, R53999, N58829, W86429, AA024852, AA101582, AA121348, AA135194, AA149607   |
| 17 | HPTWC08 | 27  | 396380 | T77302, R21500, R35136, R41732, R42882, R49522, R41732, R42882, R49522, H20938, H41732, R85141, R88669, R88670, R88816, R89638, R89643, R90743, R90777, R90782, AA040665, AA127052   |
| 18 | HRGCZ46 | 28  | 400796 | T48000, T49441, T62059, T65112, T65179, T92082, T78688, T79315, T83158, T85864, R15724, R17015, R18665, R22674, R45966, R45966, H24497, H27416, H44475, N50917, N94040, W17223, W40134, W92875, W94259, W94444, W94673, W94957, W95142, W95598, W95853, N89726, AA045010, AA081572   |
| 19 | HSVU34  | 29  | 724060 | T52500, T67115, T67116, T90451, R10617, R10618, T82973, H05156, H10930, H10931, H56169, H56385, H66700, H66701, H73933, H74126, N32119, N57071, N59463, N67109, N71110, N74124, N74136, W02046, W05471, W19600, W23443, W24737, W35258, W37178, W57794, W58026, W81529, W81530, AA079135, AA121270, AA121423, AA151481, AA151504, AA220993, AA226857, AA250826, AA252645, AA428383   |
| 19 | HSVU34  | 220 | 396807 | T52500, T67115, T67116, T90451, R10617, R10618, T82973, H05156, H10930, H10931, H56169, H56385, H66700, H66701, H73933, H74126, N32119, N57071, N59463, N67109, N71110, N74124, N74136, W02046, W05471, W19600, W23443, W24737, W35258, W37178, W57794, W58026, W81529, W81530, AA079135, AA121270, AA121423, AA151481, AA151504   |
| 20 | HSDFW61 | 30  | 407496 | T55525, R10577, R10576, R11610, T78468, T78545, T95431, R01101, R19400, H55969, H84552, N24342, N26542, N35654, N39425, N48541, N64022, N73360, N78008, N95084, W23486, W67558, W67606, W69403, W73515, W73497, W74493, W79090, N89865, AA015719, AA034158, AA053058, AA053402, AA127181   |

|    |         |     |        |   |
|----|---------|-----|--------|---|
| 22 | HSOAJ55 | 32  | 829668 | T90006, R09378, R09379, R12195, T82827, T84829, R23136, R23137, R23150, R23149, R23901, R23902, R35690, R39919, R49327, R49327, H08646, H08645, H52709, H52986, H67120, H81426, H97481, N20907, N31009, N51872, N51878, N54463, N76574, W37292, W37826, AA052963, AA053019, AA053505, AA129021, AA129020, AA133655, AA133656, AA130953, AA573417, AA746147, AA879142, AA938486, D82776, D82683, W23236, C17493  |
| 22 | HSOAJ55 | 221 | 361281 | T90006, R09378, R09379, R12195, T82827, T84829, R23136, R23137, R23150, R23149, R23901, R23902, R35690, R39919, R49327, R49327, H08646, H08645, H52709, H52986, H67120, H81426, H97481, N20907, N31009, N51872, N51878, N54463, N76574, W37292, W37826, AA052963, AA053019, AA053505, AA129021, AA129020, AA133655, AA133656  |
| 24 | HSXAM05 | 34  | 396445 | H41055, H86278, H86277, N36167, N49355, N99253, W30680, AA187548  |
| 25 | HSXAS67 | 35  | 396441 | R43052, R46024, R54365, R46024, R59349, H29581, AA018134, AA128286, AA165397  |
| 26 | HTDAF28 | 36  | 396835 | R32754, R65808  |
| 30 | HTPBW79 | 40  | 581435 | T58875, T69236, R12437, R13448, R37325, R37361, N52277, W38735, W72124, AA009696, AA088448, AA181149, AA181148  |
| 30 | HTSEV09 | 223 | 396459 | T54203, T58875, T69236, R37325, R37361, R72050, N52277, N59026, N72929, W38735, W72124, W77848, AA009696, AA009415, AA088448, AA088502, AA181149  |
| 31 | HJPCD40 | 41  | 401227 | R01078, H47562, H58468, N31052, N92318, N93676, N93667, W24390, W79518, W79405, W86336, W95427, W95554, AA002106, AA005054, AA009752, AA009751, AA022648, AA022637, AA035194, AA143435, AA157417  |
| 33 | HTWCI46 | 43  | 407490 | T71107, R07491, R07544, R02367, R02473, R12602, R74032, R74123, R79290, R81173, R81277, R86952, H49320, N54909, AA196897  |
| 34 | HTXGI75 | 44  | 396652 | H11517, H61199, H96603, N24777, N28311, N28909, N73009, N73300, W02991, W16442, W23776, W35231, W39312, W79539, W79620, AA026925, AA026924, AA079258, AA079257, AA085612, AA112862, AA143350, AA143349, AA147394, AA147466, AA147465, AA156313  |
| 35 | HWTBF59 | 45  | 740670 | T47527, T47528, T89276, T84349, R00444, R00445, R50263, R50726, R51643, R62425, R73541, H05078, H38730, H68907, H68809, H75646, H75453, H75452, H81932, H82027, N32427, N36140, N37025, N42766, N44144, N52649, N56850, N68925, W02115, W03625, W15447, W20382, W32576, W35117, W39632, W44562, W47604, W69467, W69551, W73740, W86128, W86148, W95672, AA024821, AA024927, AA025859, AA025860, AA046830, AA046873, AA126258, AA134986, AA135083, AA150759, AA150682, AA235603, AA236621, |

|    |         |     |        |   |
|----|---------|-----|--------|---|
|    |         |     |        | AA236897, AA464236, AA419070, AA419131, AA428777, AA429067, AA428056  |
| 35 | HWTBF59 | 224 | 361287 | T47528, T89276, R00445, R50726, R51643, R62425, R73541, H05078, H38730, H68907, H75646, H75453, H81932, N32427, N36140, N37025, N52649, N56850, N68925, W02115, W15447, W20382, W32576, W39632, W44562, W69551, W73740, W86128, W86148, W95672, AA024821, AA024927, AA025859, AA025860, AA046830, AA126258, AA134986, AA135083, AA150759  |
| 36 | HADAE74 | 46  | 409832 | T46989, T46988, T65134, T65203, R17426, R23237, R23312, R42660, H60654, H75862, H75861, N24093, N31388, W56001, W56290, AA047063, AA047064, AA046111, AA046198, AA098961, AA098828, AA182785, AA187777, AA191047  |
| 38 | HATEF60 | 48  | 410124 | T64995, R17261, R41876, R68452, R68454, H21498, H98622, N25142, N30676, N33908, N67489, N99057, W30718, AA035240, AA035318, AA043654, AA043655, AA046927, AA046984, AA133159, AA133204, AA131580, AA131629, AA132763, AA132857  |
| 39 | HBMSN25 | 49  | 412010 | R34536, R49053, R85085, R87831, R87846, AA199833  |
| 40 | HCDAR68 | 50  | 411482 | H24669, AA055330, AA055927  |
| 41 | HCE3J79 | 51  | 409610 | T66611, T81694, R15985, R44533, R50983, R52279, R52280, R54333, R46724, R44533, R61702, R63949, R64049, R72902, R73540, H42845, H43343, H43397, H44022, H44570, H44569, H59659, H74011, H75604, N53399, W60971, W61218, AA024497, AA024619, AA132738, AA173154, AA188369, AA237026  |
| 42 | HMDAN54 | 52  | 411318 | T78112, R19702, R37848, R44258, R44258  |
| 43 | HCECA49 | 53  | 409543 | T48789, T48790, T52689, T52690, T54143, T57627, T60334, T63169, T64611, T68165, T73770, R09683, R05784, R05870, R23705, R24243, R25436, R26263, R26661, R31482, R33617, R52663, R55790, R64491, R65588, R66756, R74348, R74447, R77767, R77861, H24648, H24647, H25483, H30170, H42201, H61272, H74187, H73366, H84457, H96852, H97161, N21258, N24067, N25891, N32256, N35943, N39665, N59887, N74237, N75946, N77028, N91815, N94382, W16791, W37991, W42625, W42503, W42504, W45097, W46997, W47010, W47011, W47035, W58226, W60191, W74239, AA011342, AA053421, AA053142, AA069730, AA069687, AA071401, AA079362, AA088476, AA088867, AA099339, AA098900, AA099401, AA099509, AA099626, AA100481, AA111899, AA112344, AA128689, AA130068, AA130069, AA133988, AA134388, AA130699, AA131164, AA135908, AA143614, AA148147, AA151655, AA151855, AA150148, AA152217, AA150454, AA156656, AA156942, AA158064, |



|    |         |     |        |  |
|----|---------|-----|--------|--|
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| 45 | HCESF40 | 55  | 616396 | R13472   |
| 45 | HCESF40 | 225 | 411082 | R13472, R37382, H49570, N55573   |
| 46 | HCFMV39 | 56  | 410579 | R91923, R92247   |
| 48 | HCNAP62 | 58  | 411042 | H21798, AA149965   |
| 49 | HCRAF32 | 59  | 409522 | AA194845   |
| 53 | HE2AV74 | 63  | 411019 | R33678, R35656, R37491, R56683, H14646, H61361, H62387, AA131445, AA131558   |
| 54 | HE2AY71 | 64  | 396403 | T67822, T67974, T73185, T67263, T67264, T91311, T84892, T85089, R22026, R22079, R23310, R25617, R31409, R33081, R33171, R33622, R33733, R48174, R48558, R48654, R66621, R73320, R73769, R74211, R74309, R82212, R82268, R82548, H03235, H03847, H19922, H46963, H46964, H47061, H47135, R91968, R94507, R94914, R94997, R98001, R99462, R99463, R99524, R99525, R99727, H48529, H48701, H53102, H54578, H57772, H59377, H61224, H61728, H62607, H65068, H65067, H66144, H66346, H66396, H66561, H67023, H67024, H67947, H68317, H68316, H70368, H75943, H78688, H78690, H78771, H78772, H78871, H79256, H79366, H85283, H94696, H98582, H98844, H99986, N20645, N24174, N25213, N26654, N29017, N30434, N33496, N36055, N39390, N39804, N42325, N43023, N43886, N44135, N44905, N55434, N58351, N58498, N59566, N68659, N72973, N73562, N74053, N74661, N75286, N76807, N77719, N78566, N80677, N93248, N93543, N98928, N98927, W00492, W00999, W01748, W04563, W04661, W05686, W07160, W07727, W17036, W20423, W20166, W20366, W21351, W23644, W31155, W31425, W33072, W35181, W37772, W37773, W39698, W45053, W45703, W44350, W46232, W46853, W55895, W55894, W57879, W57878, W72198, W73477, W73549, W92689, W94064, W94065, W94685, W95191, W95291, N89780, N89860, N90540, N91134, AA026253, AA026254, AA026166, AA029566, AA034238, AA037765, AA046097, AA053931, AA062822, AA082444, AA085263, AA085327, AA128794, AA128795, AA147331, AA191231, AA195440 |
| 55 | HE2GS36 | 65  | 779386 | N31459, AA027911, AA045421   |
| 55 | HE2GS36 | 226 | 411492 | R41228, H09131, H09953, N25344, N52068, AA027855, AA045315   |
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| 61 | HELDY74  | 71  | 410281 | T66450, R15824, R51635, W72803   |
| 62 | HEMAE80  | 72  | 409495 | T71556, T90634, T82005, T83161, H57113, H61567, AA233071   |
| 63 | HFEBA88  | 73  | 411999 | T97504, R01753, H52246, N26214, N50118, N64701, N94589, W23796, W60801, W60932, AA004342, AA063605   |
| 64 | HFGAB89  | 74  | 408358 | T89093, R60840, H16750, H51569, H51939   |
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| 67 | HGBBQ69  | 77  | 409617 | R05775, R05861, R79705, R79706, H14866, H17904, H39588, H40018, H64593, H64594, H64595, H64596, H64613, H64614, H64628, H65957, H65958, H65968, H65967, H66164, H66165, H66166, H66167, H66172, H66173, H66188, H66189, N22434, N59533, N62574, N78274, W61276, W61277, W94640, W92528, AA011621, AA011622, AA040070, AA040101   |
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| 71 | HHGCN69  | 81  | 409956 | R71890, R71889, H37817, H37868, N66068, N95661   |
| 72 | HHGDO13  | 82  | 410173 | R25955, R36307, R49238, R49238, H03251, H03252, H18871, H18870, H48152, H49465, H49464, H49937, H49940, H85293, N26655, N27044, N29702, N39238, N46682, N51027, N51035, N51042, N56710, N73444, N95391, W25227, W32932, W35368, W68062, W68063, W73332, W73353, W93595, W95726, W95769, AA025052, AA025053, AA032241, AA033649, AA151421, AA151422, AA179342, AA179574, AA180170, AA180169, AA186911 |
| 73 | HHPFD63  | 83  | 410143 | T75205, R45275, R51873, R54265, R45275, H14061, H14062, H14273, H17115, H17220, H18846, H18847, R85199, R87978, R90826, W73916, W77979, AA169431   |
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| 80 | HNFAB54  | 90  | 408120 | AA026479, AA081127, AA081152   |

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| 87 | HOGAR52 | 97  | 410161 | T81323, T81852, R01268, R01382, H27407, H28601, H79267, H79378, N58730, N62405, N71255, N72641, W01562, AA044699, AA055259, AA055258, AA082848, AA086241, AA088679, AA112191, AA156048, AA157459, AA204677   |
| 88 | HOSBZ55 | 98  | 410145 | R70745, H20568   |
| 89 | HOSDI92 | 99  | 617570 | R94013, H84608, H98837, N33140, W02553, AA004952, AA429052   |
| 89 | HOSDI92 | 230 | 410140 | T75079, R94013, H84608, H98837, N33140, N92104, W02553, AA004952, AA004951   |
| 91 | HPCAL49 | 101 | 411321 | N66498   |
| 92 | HPFCR13 | 231 | 371352 | R00702, R00703, R79938, R80028, N75501, N99910, W05126, W25289   |
| 93 | HOFNZ45 | 103 | 607449 | T51015, T51107, T59404, T59450, T89720, T93308, T67002, R00844, H40516, H43373, H43387, H96409, H99093, N47247, N47248, N53526, N62173, W94497, AA029586, AA043434, AA043435, AA188515   |
| 93 | HPHAC83 | 232 | 411468 | T51015, T51107, T55000, T55166, T57093, T57163, T59404, T59450, T69888, T70216, T89720, T89817, T93308, T93985, T67002, T67003, R00844, R01497, R74457, R74556, H02934, H04237, H05269, H27375, H27811, H40516, H38091, H43373, H43387, H44626, H46401, R92096, R95179, R95671, R97192, R97193, H50947, H86131, H86438, H96047, H96409, H99093, N20096, N22174, N22574, N22684, N23774, N24145, N26964, N27840, N27867, N27902, N29227, N29232, N29808, N31162, N36009, N36131, N40614, N40642, N44138, N44243, N47247, N47248, N51254, N53526, N53972, N59053, N62173, N67339, N67385, N71220, N75793, N79303, N91802, W04949, W31236, W47342, W52023, W57583, W68144, W68471, W74547, W74488, W79753, W80606, W80607, W94497, W94496, AA013048, AA013341, AA029585, AA029586, AA039227, AA043434, AA043435, AA047188, AA064949, AA064950, AA076086, AA076183, AA125863, AA125862, AA128872, AA134540, AA148819, AA150288, AA150419, AA167118, AA173560, AA173724, AA186892, AA188515, AA232090, AA235715 |
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| 95 | HPWAN23 | 233 | 411353 | R11595, R18735, H03839, H03838, H09030, AA114200, AA147186, AA147297   |
| 96 | HRDFB85 | 106 | 411020 | R12121, T96099, R05961, R05962, R36883, R48403, R50075, R50076, H13937, H27324, H27350, H44304, H93341, H93844, N72688, W02467, W21446, W74492, W79089, AA149303, AA149402, AA149417, AA149738, AA157596, AA157892   |
| 97 | HRGBR28 | 107 | 410144 | T74132, R19091, H16341, H16424, R87393, W74106, AA120808, AA160124   |
| 98 | HSKGN81 | 234 | 409905 | T64523, T65948, T74373, R12726, R17501, R27706, R42595, R42595, AA031630, AA082483,  |

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| 99  | HSPA56  | 109 | 411538 | R10761, R46703, R46703, N51835, AA115766, AA127238, AA156859   |
| 100 | HE8EU04 | 110 | 686925 | T59099, T89118, T89207, T98083, R06017, H43963, H43962, N27605, N31860, N42656, N48371, N81110, W01192, W24031, W31758, W69603, W79669, AA227693, AA227676, AA262822   |
| 100 | HSXBT86 | 235 | 410177 | T59099, T89116, T89118, T89205, T89207, T98005, T98083, R06017, H01422, H28038, H39525, H43963, H43962, N22985, N23959, N31597, N31860, N32689, N38734, N40651, N42656, N48371, N53027, N62930, N81110, N98486, W01192, W16833, W24031, W24259, W31758, W52828, W69414, W69603, W72795, W74131, W76117, W78992, W79669, W80618, W93298, W92848, AA027834, AA027877, AA065180, AA065181, AA156606, AA156909, AA173551, AA173717, AA173998, AA176694, AA227693, AA227676, AA235938, AA236953 |
| 101 | HSXCS62 | 111 | 410342 | R14929, R35412, R41243, R49209, R41243, R49209, H09440, H24724, H24725, H25649, H25822, H41130, H45960, H46504, H47042, R84480, R85875, R89720, R89721, H56511, N28648, N31600, N34149, N36302, N42659, W32884, W35153, AA135837, AA135998   |
| 102 | HTEFU09 | 112 | 410283 | T53177, T98847, R20208, R47997, R48112, R53403, R53996, R74086, R74085, H52255, H58876, N24921, N33797, N41673, N69460, N70571, W04529, W20201, W31409, W85735, W85802, W95123, W95240, N90952, AA016215, AA021506, AA025099, AA025188, AA037648, AA037649, AA053008, AA160015, AA188552   |
| 105 | HTGEW91 | 115 | 411467 | T75409, R12833, R20743, R51579, R51668, R20743, R70022, R70067, H13081, H13285, H20181, H20372, H94368, N24535, N24564, N25423, N25546, N33976, N34007, N34115, N34143, AA082676, AA128130, AA125885, AA150041, AA150157, AA167115, AA167271, AA188416, AA188618, AA188719, AA188737, AA194567, AA227181, AA236511   |
| 106 | HTOEY16 | 116 | 411419 | T77313, R18801, R43911, R43911, R78272, R78273, H99299, H99300, N25845, N36152, N36173, N44152, N44162, W02226, W32550, AA057265, AA058710, AA085565, AA182006, AA235467   |
| 108 | HTSGM54 | 118 | 792952 | T57851, T82405, R10508, T81626, R14860, N64170, AA114906, AA114905, AA233797, AA233828   |
| 108 | HTSGM54 | 236 | 411477 | T57851, T82405, R10508, T81626, R14860, N64170, AA114906, AA114905, AA233797, AA233828   |
| 109 | HTSHE40 | 119 | 411287 | R49564, R49564, H72036, W90622   |
| 111 | HTWBY29 | 121 | 410175 | T59381, R19528, R43882, R43882, R55664, R55665, H17451, H17555, R88491, R90802, R90803, AA019030, AA021487, AA080905,  |

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| 112 | HUKFC71  | 122 | 410328 | H40724, H46968, N42261, W31201, W31772, W74161, AA078878, AA147783, AA155778   |
| 113 | HCE3Q10  | 123 | 412333 | R12129, R15338, R36062, H08308, H14720, H40798, H38530, R88252, R88963, N45514   |
| 114 | HCEVR60  | 124 | 414534 | T94052, R63094, R63141, W72684, W73520, W73503, W77790, AA075563, AA075558   |
| 115 | HDTAW95  | 125 | 412472 | R46762, R46857   |
| 117 | HELBU29  | 127 | 414535 | H18640, N66514, N98666, AA224105, AA232976, AA233279, AA256848, AA256892, AA256170, AA256228, AA256376, AA256436   |
| 120 | HHPTD20  | 130 | 371716 | H04828   |
| 121 | HIBED17  | 131 | 412488 | R50692, R70201, R70202, R73362, H05522, H10062, H10116, H12934, H68642, H68643, N22739, W60865, W60941, W81135, W81134, AA029699, AA029640, AA056576, AA056680, AA129131   |
| 123 | HOABL56  | 133 | 413244 | R79757, R79756, R92799, R95927, H54516, H83042, N20295, N26162, N27565, N55348, N62316, N77354, N79565, W16550, AA017055   |
| 124 | HPMCJ92  | 134 | 399492 | R77437, R77527, H01511, H01617   |
| 128 | HUKCO64  | 138 | 413200 | T90943, T79172, T79255, T84324, T85824, T95309, T95390, T99391, R30896, R60293, H58319, H58709, H72088, H72189, H73940, H79782, H79816, H79875, H79910, AA043890, AA045424, AA171926   |
| 129 | H6EAA53  | 139 | 103314 | T71026, T71027, T71089, T74115, T74491, T92559, T92631, R31026, R31516, R36638, R47741, R50388, R56704, R79276, R82645, H15896, H16001, H19629, H19628, H19840, H21086, H21123, H21218, H24606, H25286, H25326, H30481, H41893, H41894, H37793, H45153, H45281, H45351, R94255, R94615 |
| 132 | HALSK07  | 142 | 418461 | T82404, R24457, N51926, N53706, AA136333, AA136419   |
| 133 | HALSQ59  | 143 | 396185 | AA075298   |
| 134 | HAIBP89  | 144 | 727543 | T69855, R08029, R08078, H08338, H08339, H24045, H24152, H42902, H42973, H58361, H58750, H80028, H94211, N70685, N99825, W42711, W42904, W57667, W60487, W60773, AA009753, AA135410, AA135816, AA258159, AA258978   |
| 134 | HBGCB91  | 237 | 371337 | T69855, R08029, R08078, H08339, H24045, H42902, H42973, H58361, H58750, H80028, H94211, N70685, N99825, W42711, W42904, W57667, W60487, W60773, AA009753, AA135410   |
| 135 | HBM TD81 | 145 | 410544 | R21916, R22565, R99043, AA046203, AA046283, AA055141, AA173411, AA173467   |
| 136 | HBXGK12  | 146 | 415649 | T55067, R05951, R76538, R76945, R77034, R79544, R79545, H00668, H61203, H62107, N74280, N77879, W04380, W05836, W07303, AA026385, AA026375, AA047358, AA055622, AA112556, AA159861, AA255749   |
| 137 | HFKFJ07  | 147 | 423130 | AA152460   |
| 138 | HCQAI40  | 148 | 411145 | T95631, AA005342, AA004292, AA022666,  |

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| 141 | HE8BY43 | 151 | 407475 | R74382, R74394, H24509, H89226, N22621, W37881, W37943, W76005, AA215347   |
| 142 | HFCEB37 | 152 | 411345 | H06701   |
| 143 | HFTCT67 | 153 | 412026 | H40744, N94366, AA187325, AA188450   |
| 144 | HGLAM46 | 154 | 408366 | T49176, T49177, R23545, R44296, R48547, R48636, R44296, R70950, R71001, R77003, H01174, H01262, H04151, H04152, H40131, R98874, R98963, H58076, H58099, H59475, H61466, H65722, H65723, H74292, H74293, H83754, H83896, H91603, H91602, H93008, H94999, H98174, H99350, N20932, N21320, N22996, N23788, N24183, N24199, N24913, N26462, N27800, N28582, N31255, N31663, N31686, N32064, N32421, N32703, N36039, N41352, N42221, N45375, N56843, N70498, N70787, N93093, W01403, W24405, W40392, W45383, W48824, W51970, W72864, W75959, W78937, W85704, W86916, AA011569, AA036893, AA127482, AA127481, AA146840, AA146841, AA150457, AA156659, AA159754, AA159753, AA171950, AA172157, AA179486, AA179508, AA179528, AA179539, AA190735, AA196875 |
| 145 | HHGBR15 | 155 | 214364 | R39009, R41924, R41924, R59390, N22125, N68556, AA036728   |
| 146 | HJAAU36 | 156 | 414157 | T39986, T93486, T96316, T67465, T69498, T72660, T72729, T86380, T86281, T98445, T98500, T99806, T99911, R79809, R79909, H26813, H27797, H28014, H28191, H28234, R83661, R83660, R83673, R83674, R83685, R83686, R86297, R86296, R86312, R86311, H51032, H51031, H52549, H60248, H80916, H88268, H88269, N62947, N63163, N79850, W20040, W72762, W74448, N91378, AA102584, AA232099, AA232534, AA232806, AA233861, AA235866, AA236068   |
| 147 | HUSIT49 | 157 | 421065 | T66884, R54992, R55445, H19850, H21231, H22646, H22647, H27769, H27834, H42917, H42918, H43624, H44676, R88710, R90960, R92816, R96930, R96986, R98590, R98589, H60171, H95774, H96129, N54424, N58406, AA129135, AA129134, AA176131, AA195034, AA262891   |
| 148 | HKLAB16 | 158 | 419037 | R02500, R32757, R37842, R70640, R82407, W32933, W35369, N90561, AA026880,  |

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|     |          |     |        | AA057127, AA057193   |
| 149 | HLMMU76  | 159 | 413374 | T59668, T59802, W73105, AA160748   |
| 150 | HMSKQ35  | 160 | 415560 | R53057, H82270, N51427, AA021420, AA026971, AA026972   |
| 154 | HOECU83  | 164 | 831917 | R34106, R34105, AA166983, AA224458, AA531249, AA588629, C21057   |
| 154 | HOECU83  | 238 | 419012 | R34106, R34105, AA224458   |
| 155 | HPTRC15  | 165 | 418375 | T90946, T85832, R15053, R60917, R61036, R68361, H05094, H05556, H06465, H10224, H10280, H10972, H10973, H22893, N28604, AA011623, AA011624, AA016231, AA026059, AA166886   |
| 156 | HSKCP69  | 166 | 702021 | R09234, R09346, R06914, R06965, H68486, H75419, N67047, W00859, AA029670, AA044243, AA044324, AA148822, AA150422   |
| 156 | HSKCP69  | 239 | 413210 | R09234, R09346, R06914, R06965, H68486, H75419, N67047, W00859, AA029670, AA044243, AA044324, AA148822, AA150422   |
| 157 | H6BAE26  | 167 | 422804 | AA182585, AA243086   |
| 160 | HAICP19  | 170 | 422672 | T39496, T49219, T49220, N31961, N31991, W04672, W31773, AA120830, AA120831   |
| 161 | HAUAE83  | 171 | 422695 | T47437, T47436, T47523, T48820, T48821, T53678, T53679, T54444, T54498, T60151, T60211, T63582, T64428, T65689, T65699, T92720, T92800, T74745, T90117, T82456, T82942, T83431, T84078, R19785, R23160, R24260, R24366, R33337, R35278, R36040, R36975, R49121, R50949, R52419, R53809, R53853, R49121, R56655, R56823, R58965, R59021, R63366, R63415, R64167, R64282, R66836, R66884, R67802, R67803, R67933, R67969, R75720, R78064, R80262, R80377, R81338, R81590, H01186, H01282, H08184, H08284, H08404, H08405, H29026, H45836, R97102, R97149, H50658, H50748, H56041, H56118, H65070, H68501, H70503, H88218, H88217, H93598, H93618, N20946, N23947, N27815, N31848, N40220, N51513, N53182, N66179, N66807, N66808, N69755, N98422, N99170, W03608, W38501, W39785, W45318, W46310, W46309, W47477, W47478, W58724, W60790, W60789, W84314, W84341, W94553, W92626, AA022581, AA022582, AA026348, AA026576, AA027051, AA033709, AA034334, AA046827, AA046826, AA045549, AA045550, AA127720, AA127775, AA143073, AA143133, AA150844, AA151016, AA192781, AA192782 |
| 163 | HBMTY28  | 173 | 422688 | T54996, T55162, T81957, H40448, H40449, R96511, R96556, H59080, H60352, N58089, N76050, W04455, AA005161, AA004218, AA011395, AA011432, AA116050   |
| 164 | HBMVP04  | 174 | 812281 | H82435, H82698, N53899, W04955   |
| 164 | HBMVP04  | 241 | 419854 | H82435, H82698, N53899, W04955   |
| 165 | HCDDDB78 | 175 | 422696 | T80138, R05721, R05722, R40720, R51388, R40720, R60772, H77587, H91710, H91811, N52332, N62896, N75102, W01336, W24829,  |

|     |         |     |        |  |
|-----|---------|-----|--------|--|
|     |         |     |        | W56236, W78702, W80502, AA031936, AA031937, AA034077, AA046609, AA046724, AA129906, AA129905, AA133809, AA150149, AA152218, AA235941, AA236885   |
| 167 | HCEZS40 | 177 | 422714 | R12037, R18992, R44878, R44878, H56172, H56388, H58079, H79475, H97586, N20466, N25493, N28755, N50120, N62820, W01355, W74545, W74486, W93543, AA128184, AA126379   |
| 168 | HCFNF11 | 178 | 422712 | H80152, AA010492, AA167414, AA167418, AA167415, AA167426, AA167425, AA167419, AA171736, AA172019   |
| 169 | HCRBL20 | 179 | 744946 | T89241, H88386, H88454, H88386, N46536, N63060, W93935, W93936, AA075562, AA075557, AA180173, AA180147, AA194932, AA194931, AA194884, AA195588, AA213530, AA243504, AA243357, AA422037   |
| 169 | HCRBL20 | 242 | 422383 | T89241, H88386, H88454, H88386, N46536, N63060, W93935, W93936, AA075562, AA075557, AA180147, AA194932, AA194931, AA194884, AA195588, AA213530, AA243504, AA243357   |
| 171 | HDSAP81 | 181 | 422719 | N39609, AA011604   |
| 172 | HE2CT29 | 182 | 420020 | N74326   |
| 173 | HE8MG65 | 243 | 422740 | T56650, T57256, T63714, T73914, T73938, T73946, T73970, T77203, R22170, R22171, R24271, R24380, R27064, R27990, R28253, R28546, R33988, R39548, R60886, R66279, R66278, R67307, R71201, R71202, H02943, H03083, H03084, H04243, H04760, H04851, H06938, H06939, R84922, R91805, R91804, R93954, R93953, R94083, R94129, H52707, H69823, H69832, H84985, H87352, H87893, H94285, N24258, N26510, N31711, N33488, N35085, N35563, N42365, N43879, N53729, N67539, N73915, N77452, N78653, W45116, W78900, W84673, AA015592, AA018305, AA018631, AA018727, AA019837, AA022837, AA022960, AA039983, AA040630, AA156047 |
| 174 | HE9FB42 | 184 | 828253 | T71135, T81630, T82274, T83563, R66636, H04574, H18490, N46661, N47628, N52212, N53127, N53634, N62209, N66750, N76507, N79940, W73330, W84546, AA149684, AA164834, AA164833, AA171498, AA171599, AA187239, AA187687, AA187903, AA186756, AA227149, AA227342, AA233128, AA233262, AA233728, AA258430, AA259060, X93861, AA603886, AA568710, AA639952, AA974278, W26196, W84460, C20754, AA090438, AA094076   |
| 174 | HE9FB42 | 244 | 420024 | T71135, T81630, T82274, T83563, N46661, W73330, AA149684, AA164833, AA171599, AA187239, AA187903, AA186756, AA227149, AA227342   |
| 175 | HEMAM41 | 185 | 741647 | R40658, R40658, N62855   |
| 175 | HEMAM41 | 245 | 419870 | R40658, R40658, N62855   |
| 176 | HEMCV19 | 186 | 423219 | R39576, R39644, R55519, R55520, H25585,  |



|     |         |     |        |  |
|-----|---------|-----|--------|--|
|     |         |     |        | H25630, H42497, H43485, R95168, H73675, H73419, H80718, H80719, W95391, W95348, AA034079, AA044081, AA187305, AA187096   |
| 178 | HETAR54 | 188 | 422765 | R22877, R78124, H86507, N34893, N95529, W20289, W24342, W32533, W32670, N90669, AA019416, AA019318, AA026402, AA027311, AA037586, AA054647, AA252682   |
| 179 | HETBX14 | 189 | 806447 | W60282   |
| 179 | HETBX14 | 247 | 422659 | W60282   |
| 180 | HFGAB48 | 190 | 422777 | R42520, R42520, N64660, N80095   |
| 181 | HFKFI40 | 191 | 423226 | T47877, T47937, T51505, T75501, T89199, T85240, T85406, R20055, R28467, R31273, R31879, R76266, H03224, H04016, H16963, H30109, N53759, N58780, N62962, N77467, N79865, N81078, W07419, W57548, W68669, W68772   |
| 182 | HFHXN68 | 192 | 422549 | T87904, T87997, R10903, R10955, H64853, N63499, N74353, N74407, N94712, W02620, W03115   |
| 183 | HGBFO79 | 193 | 422794 | T74861, R54514, R76898, R77063, R79667, R79856, R84453, R98071, H54089, W40292, W46517, W88866, AA203205   |
| 184 | HGLAM56 | 194 | 423223 | AA256641, AA256642   |
| 187 | HHPSD37 | 197 | 422805 | R44397, R44397, N32549, N41894, AA085999   |
| 188 | HHPSF70 | 198 | 422809 | R26136, H08855, H41065, H55993, H80007, H83746, H83889, H88534, H88580, H89097, H89200, N22006, N45466, N45508, N51670, N51854, N54118, N62627, N71208, N78398, AA018235, AA019116, AA131865, AA131952, AA148774, AA148523   |
| 189 | HHSK25  | 199 | 422813 | T92909, T93001, T95997, R61024, H19116, H24430, H24459, R94331, H67161, H68562, H73892, H73918, H74085, H74110, H78993, H81466, H81767, H81766, H82583, H91720, H91821, H99152, N20388, N22843, N24401, N24496, N25453, N28651, N35075, N36359, N43815, W92746, W92869, AA057815 |
| 190 | HIASB53 | 200 | 422811 | T68050, R97204, N42257, AA046836, AA047007, AA157267, AA157180, AA186993, AA188308, AA196715   |
| 191 | HJABZ65 | 201 | 419857 | N75833, N78710, N91897, W44720, W44764, N90606, AA135838   |
| 192 | HJPBB39 | 202 | 422649 | T66427, R15801, R14623, R33639, R45609, R51011, R51118, R45609, R66101, R67704, H17989, H17990, N94819, W17083, W67749, W68029, W74094, W79385, W94890, W92054, AA007307, AA007469, AA054550, AA054558, AA054610, AA054618, AA054521   |
| 193 | HLHSK94 | 203 | 422828 | R55809, H83295, N92239, W37154, W38638, N90902, AA017680, AA040604, AA040705   |
| 194 | HLHTC70 | 204 | 422829 | R61522, H08810   |
| 196 | HLTCY93 | 206 | 422848 | T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, AA005068, AA007333, AA007334, AA036884, AA044715, AA044907,  |

|     |         |     |        |  |
|-----|---------|-----|--------|--|
|     |         |     |        | AA045458, AA046500, AA045654, AA115936, AA126775, AA133605, AA133606, AA133980, AA181633, AA182611   |
| 197 | HLTDB65 | 207 | 419864 | T88814, T78480, T78565, T84197, T96608, T96718, T96898, T96899, R01674, R02614, R62952, R63004, H01169, H01254, H40397, H53915, H54535, H86324, N23958, N28602, N31859, W17062, W40144, W49624, N89648, AA019070, AA019151, AA134914, AA136931, AA137028, AA148976, AA148977, AA196164, AA196293   |
| 199 | HMSHQ24 | 209 | 422565 | R16159, R55052, R59723, R72647, H60244, N33957, N79519, N79654, AA032239, AA033647, AA156948   |
| 200 | HNFAH08 | 210 | 420031 | R62825, H69909, H69910, H69910, N25612, N34210, AA056610, AA251839, AA251814   |
| 205 | HOSFM22 | 215 | 412025 | T90315, T90402, R23872, R30787, R76172, R77141, R80565, H00726, H01049, H01153, H04603, H04630, H12817, H79113, H82795, H95178, N42743, N68145, N75220, N94419, N98917, W19432, W30766, W31142, W46805, W46923, W48861, W79735, W92123, AA046579, AA046665, AA046966, AA057191, AA127892, AA129011, AA136002, AA136874, AA136903, AA152237, AA152204, AA199930, AA203584 |
| 206 | HPHAC88 | 216 | 411423 | R19567, R35876, R35877, R48573, R48673, H41417, R85943   |
| 207 | HCDEO95 | 217 | 371706 | H69632, H70475, N66605, AA026327   |

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

## 5        Examples

### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector.

10    Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being

15    isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

|    | <u>Vector Used to Construct Library</u> | <u>Corresponding Deposited</u> |
|----|---|--------------------------------|
|    | <u>Plasmid</u>                          |                                |
|    | Lambda Zap                              | pBluescript (pBS)              |
| 20 | Uni-Zap XR                              | pBluescript (pBS)              |
|    | Zap Express                             | pBK                            |
|    | lafmid BA                               | plafmid BA                     |
|    | pSport1                                 | pSport1                        |
|    | pCMVSport 2.0                           | pCMVSport 2.0                  |
| 25 | pCMVSport 3.0                           | pCMVSport 3.0                  |
|    | pCR <sup>®</sup> 2.1                    | pCR <sup>®</sup> 2.1           |

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos.

30    5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are

commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

- 5            Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ - $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).)
- 10        The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate.
- 15        These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

- Alternatively, two primers of 17-20 nucleotides derived from both ends of the
- 20        SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu\text{l}$  of reaction mixture with 0.5  $\mu\text{g}$  of the above cDNA template. A convenient reaction mixture is
- 25        1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20  $\mu\text{M}$  each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and
- 30        the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

**Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X.,  
5 according to the method described in Example 1. (See also, Sambrook.)

**Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by,  
10 among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The  
15 purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to  
20 manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

**Example 4: Chromosomal Mapping of the Polynucleotides**

25 An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C.  
30 Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose

gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide**

5 A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product  
10 into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning  
15 sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which  
20 expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid  
25 culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to  
30 increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic



agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with  
5 high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is  
10 eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear  
15 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at  
20 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains:  
25 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

30 DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA

insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

- 5       The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

**Example 6: Purification of a Polypeptide from an Inclusion Body**

- 10       The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

- 15       Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

- 20       The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

- 25       The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

- 30       Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16  $\mu$ m membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40")

is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral  
5 sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription,  
10 translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in  
15 Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell  
20 Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1%  
25 agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

30 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation

mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

5        Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a  
10   microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is  
15   then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life  
20   Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a  
25   micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

30        To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of

infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of  $^{35}\text{S}$ -methionine and 5 uCi  $^{35}\text{S}$ -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

#### **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a

selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

5       The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

10       Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 a pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are  
15       seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in  
20       6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed,  
25       for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For  
30       example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to



IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create  
5 chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

10 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion  
15 can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will  
20 not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

25

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC  
GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCC  
AAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCG  
30 TGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC  
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC  
AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG

GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT  
CCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA  
GAACCACAGGTGTACACCCTGCCCCATCCCGGGATGAGCTGACCAAGAA  
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCG  
5 CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC  
GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC  
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGA  
TGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT  
CCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

10

**Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to  
15 induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are  
20 monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures  
25 involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids,  
30 about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the

present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma  
5 cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is  
10 possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the  
15 polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed  
20 herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

25 For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al.,  
30 BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson

et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

**Example 11: Production Of Secreted Protein For High-Throughput**

5 **Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for  
10 a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and  
15 plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

20 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom  
25 plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

30 Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates

of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>-5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>-9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>-7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>-H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>-7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed

with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

- 5           The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

- 10           On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

- 15           It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### **Example 12: Construction of GAS Reporter Construct**

- 20           One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

- 25           GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with  
30 IL-12. Stat5 was originally called mammary growth factor, but has been found at

higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- $\alpha$ , IFN- $\gamma$ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

|    | <u>JAKs</u>                      |             |             |             |             | <u>STATS</u> | <u>GAS(elements) or ISRE</u> |
|----|----------------------------------|-------------|-------------|-------------|-------------|--------------|------------------------------|
|    | <u>Ligand</u>                    | <u>tyk2</u> | <u>Jak1</u> | <u>Jak2</u> | <u>Jak3</u> |              |                              |
|    | <u>IFN family</u>                |             |             |             |             |              |                              |
| 5  | IFN-a/B                          | +           | +           | -           | -           | 1,2,3        | ISRE                         |
|    | IFN-g                            |             | +           | +           | -           | 1            | GAS (IRF1>Lys6>IFP)          |
|    | IL-10                            | +           | ?           | ?           | -           | 1,3          |                              |
|    | <u>gp130 family</u>              |             |             |             |             |              |                              |
| 0  | IL-6 (Pleiotrophic)              | +           | +           | +           | ?           | 1,3          | GAS (IRF1>Lys6>IFP)          |
|    | IL-11(Pleiotrophic)              | ?           | +           | ?           | ?           | 1,3          |                              |
|    | OnM(Pleiotrophic)                | ?           | +           | +           | ?           | 1,3          |                              |
|    | LIF(Pleiotrophic) ?              | +           | +           | ?           | 1,3         |              |                              |
|    | CNTF(Pleiotrophic)               | -/+         | +           | +           | ?           | 1,3          |                              |
| 5  | G-CSF(Pleiotrophic)              | ?           | +           | ?           | ?           | 1,3          |                              |
|    | IL-12(Pleiotrophic)              | +           | -           | +           | +           | 1,3          |                              |
|    | <u>g-C family</u>                |             |             |             |             |              |                              |
| 10 | IL-2 (lymphocytes)               | -           | +           | -           | +           | 1,3,5        | GAS                          |
|    | IL-4 (lymph/myeloid)             | -           | +           | -           | +           | 6            | GAS (IRF1 = IFP >>Ly6)(IgH)  |
|    | IL-7 (lymphocytes)               | -           | +           | -           | +           | 5            | GAS                          |
|    | IL-9 (lymphocytes)               | -           | +           | -           | +           | 5            | GAS                          |
|    | IL-13 (lymphocyte)               | -           | +           | ?           | ?           | 6            | GAS                          |
| 15 | IL-15                            | ?           | +           | ?           | +           | 5            | GAS                          |
|    | <u>gp140 family</u>              |             |             |             |             |              |                              |
|    | IL-3 (myeloid)                   | -           | -           | +           | -           | 5            | GAS (IRF1>IFP>>Ly6)          |
|    | IL-5 (myeloid)                   | -           | -           | +           | -           | 5            | GAS                          |
| 10 | GM-CSF (myeloid)                 | -           | -           | +           | -           | 5            | GAS                          |
|    | <u>Growth hormone family</u>     |             |             |             |             |              |                              |
|    | GH                               | ?           | -           | +           | -           | 5            |                              |
|    | PRL                              | ?           | +/-         | +           | -           | 1,3,5        |                              |
| 15 | EPO                              | ?           | -           | +           | -           | 5            | GAS(B-CAS>IRF1=IFP>>Ly6)     |
|    | <u>Receptor Tyrosine Kinases</u> |             |             |             |             |              |                              |
|    | EGF                              | ?           | +           | +           | -           | 1,3          | GAS (IRF1)                   |
|    | PDGF                             | ?           | +           | +           | -           | 1,3          |                              |
|    | CSF-1                            | ?           | +           | +           | -           | 1,3          | GAS (not IRF1)               |



To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10        5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTT  
CCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID  
NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3'  
15 (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following  
20 sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCC  
GAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGT  
CCCGCCCTAACTCCGCCCATCCCGCCCTAACTCCGCCCAGTTCCGCCCA  
TTCTCCGCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGC  
25 CGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAG  
GCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be  
30 instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

#### **Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152),

although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4<sup>+</sup> Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred  
5 directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed  
10 in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve  
15 as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as,  
20 stable transfected cells, which would be apparent to those of skill in the art.

**Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by determining  
25 whether polypeptides of the invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

30 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and

wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing  
5 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na<sub>2</sub>HPO<sub>4</sub>·7H<sub>2</sub>O, 1 mM MgCl<sub>2</sub>, and 675 uM CaCl<sub>2</sub>. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

10 The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described  
15 growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold  
20 induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

25 When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

30 Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl

phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

- 5       The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., *Oncogene* 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

- 10       5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

- Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1  
15 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

- 20       PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and  
25 resuspended with pipetting up and down for more than 15 times.

- Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418  
30 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count  
5 the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200  $\mu$ l of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50  $\mu$ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR  
10 can be used, such as 50 ng/ $\mu$ l of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

**Example 16: High-Throughput Screening Assay for T-cell Activity**

15 NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of  
20 apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target  
25 genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in  
30 treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCCTAACTCGCCCCATCCCGCCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGC AAAAAGCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.



Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

| # of<br>plates | (ml) | Rxn buffer diluent<br>(ml) | CSPD |
|----------------|------|----------------------------|------|
| 10             | 60   |                            | 3    |
| 11             | 65   |                            | 3.25 |
| 12             | 70   |                            | 3.5  |
| 13             | 75   |                            | 3.75 |
| 14             | 80   |                            | 4    |
| 15             | 85   |                            | 4.25 |
| 16             | 90   |                            | 4.5  |

|    |     |       |
|----|-----|-------|
| 17 | 95  | 4.75  |
| 18 | 100 | 5     |
| 19 | 105 | 5.25  |
| 20 | 110 | 5.5   |
| 21 | 115 | 5.75  |
| 22 | 120 | 6     |
| 23 | 125 | 6.25  |
| 24 | 130 | 6.5   |
| 25 | 135 | 6.75  |
| 26 | 140 | 7     |
| 27 | 145 | 7.25  |
| 28 | 150 | 7.5   |
| 29 | 155 | 7.75  |
| 30 | 160 | 8     |
| 31 | 165 | 8.25  |
| 32 | 170 | 8.5   |
| 33 | 175 | 8.75  |
| 34 | 180 | 9     |
| 35 | 185 | 9.25  |
| 36 | 190 | 9.5   |
| 37 | 195 | 9.75  |
| 38 | 200 | 10    |
| 39 | 205 | 10.25 |
| 40 | 210 | 10.5  |
| 41 | 215 | 10.75 |
| 42 | 220 | 11    |
| 43 | 225 | 11.25 |
| 44 | 230 | 11.5  |
| 45 | 235 | 11.75 |
| 46 | 240 | 12    |
| 47 | 245 | 12.25 |
| 48 | 250 | 12.5  |
| 49 | 255 | 12.75 |
| 50 | 260 | 13    |

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

5 Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes

in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small  
5 molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for  
10 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four  
15 times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to  $2-5 \times 10^6$  cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are  
20 washed twice with HBSS, resuspended to  $1 \times 10^6$  cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as  
25 fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;  
30 and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

**Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of  
5 transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also  
10 membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and  
15 non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of  
20 activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from  
25 Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 µl of cell culture grade type I collagen (50 µg/ml), gelatin (2%) or polylysine (50 µg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or  
30 calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar

Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

- 5           To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM
- 10   HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane
- 15   bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.
- 20           Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a
- 25   biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- The tyrosine kinase reaction is set up by adding the following components in
- 30   order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,

pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

- 5        The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20 min. This allows the streptavidin coated 96 well plate to associate with the  
10    biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for one hour. Wash the well as above.

- Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and  
15    incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

20        **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

- As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be  
25    used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by  
30    substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are

then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any  
5 of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degrees C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the  
10 supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)  
15 antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased  
20 fluorescent signal over background indicates a phosphorylation.

**Example 21: Method of Determining Alterations in a Gene**  
**Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a  
25 phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C,  
30 using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre

Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

5        PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

10        Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the  
15        corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera  
20        (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and  
25        translocations. These alterations are used as a diagnostic marker for an associated disease.

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

30        A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus,



it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with  
5 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample  
10 containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature.  
15 The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard  
20 curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

#### 25 **Example 23: Formulation**

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a  
Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the  
30 invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to

modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable  
5 polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP  
10 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

15 Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (see generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317-327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE  
20 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. (USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than  
25 about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., N. Engl. J.  
30 Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes

(e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis.

Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered  
5 separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be  
10 administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either  
15 or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given  
20 first, followed by the second.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the  
25 Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™  
30 (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the

invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in  
5 any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott); COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott);  
10 dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead);  
15 DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'-azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of  $\beta$ -L-FD4C and  $\beta$ -L-FddC (WO 98/17281).

20 Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn);  
25 DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and  
30 Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myers Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Wellcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine receptor agonists such as RANTES, SDF-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compounds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide



reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1 $\alpha$ , MIP-1 $\beta$ , SDF-1 $\alpha$ , IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN- $\alpha$ 2a; antagonists of TNFs, NF $\kappa$ B, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targeted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al.*, *PNAS* 94:11567-72 (1997); Chen *et al.*, *Nat. Med.* 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF- $\alpha$  antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and  $\alpha$ -naphthoflavone (WO 98/30213); and antioxidants such as  $\gamma$ -L-glutamyl-L-cysteine ethyl ester ( $\gamma$ -GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

- 5 In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, 10 RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ 15 (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any 20 combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or 25 prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with 30 FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another

specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

- 5 PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

- 10 In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, 15 fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

- In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may 20 be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the 25 Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® 30 (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as

DELTAONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrexate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

5 In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™  
10 (antithymocyte globulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In certain embodiments, the Therapeutics of the invention are administered  
15 alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen,  
20 meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid  
25 derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

30 In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but

are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen  
5 Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

10 Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate  
15 including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten  
20 oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum  
25 (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the  
30 context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated

Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydropoline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; 5 Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium 10 Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase 15 inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an 20 integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; 25 Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

30 Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the

function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be

5 administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the

10 function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may

15 be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to

20 indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

25 In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in

30 combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is

contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or  
5 polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth  
10 factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be  
15 administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan),  
20 nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and  
25 Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for  
30 example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example,



Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone propionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing hormone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further

embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

5 In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more  
10 radisotopes. Particularly preferred isotopes are <sup>90</sup>Y and <sup>111</sup>In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-  
15 alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in  
20 combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPG, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma  
25 (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No.  
30 WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202),

312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor

(GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to,  $^{127}\text{I}$ , radioactive isotopes of iodine such as  $^{131}\text{I}$  and  $^{123}\text{I}$ ; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth

- hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and
- 5 METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing
- 10 hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T<sub>4</sub>™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T<sub>3</sub>™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-
- 15 *n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca<sup>2+</sup> channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).
- 20 Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or conjugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quínestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™
- 25 (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™
- 30 (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and

AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone),

5 LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-

10 NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders

15 include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™

20 and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotrophic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids

25 and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE

30 SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and

- VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate),
- 5 HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON
- 10 LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and
- 15 FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate); ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate),
- 20 DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and
- 25 ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof;

30 insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™;

oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOS™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (pioglitazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estradiol (e.g., FEMHRT™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B<sub>12</sub>, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin,



folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that  
5 may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine,  
10 divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety  
15 agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents  
20 that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g.,  
25 levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benzotropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents.  
30 Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat,

fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

#### **Example 24: Method of Treating Decreased Levels of the Polypeptide**

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

#### **Example 25: Method of Treating Increased Levels of the Polypeptide**

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically

effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

#### **Example 26: Method of Treatment Using Gene Therapy-Ex Vivo**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and

initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is  
5 maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue  
10 culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

15 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the  
20 media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is  
25 produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 27: Gene Therapy Using Endogenous Genes Corresponding To** 30 **Polynucleotides of the Invention**

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a

promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the  
5 activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous  
10 polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends.  
15 Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested  
20 with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol  
25 precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are  
30 known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide

sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub>HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V, respectively. As voltage increases, cell survival decreases, but

the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

- Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.
- The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

**Example 28: Method of Treatment Using Gene Therapy - In Vivo**

- Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.
- The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., *Cardiovasc. Res.* 35(3):470-479 (1997); Chao et al., *Pharmacol. Res.* 35(6):517-522 (1997); Wolff, *Neuromuscul. Disord.* 7(5):314-318 (1997); Schwartz et al., *Gene Ther.* 3(5):405-411 (1996); Tsurumi et al., *Circulation* 94(12):3281-3290 (1996) (incorporated herein by reference).

- The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in  
5 Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are  
10 preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies  
15 have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder,  
20 stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It  
25 is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery  
30 and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express



polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA

in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked  
5 DNA.

**Example 29: Transgenic Animals.**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters,  
10 guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

15 Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology  
20 (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the  
25 polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229  
30 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into

enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

5 The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory  
10 sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is  
15 to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only  
20 that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the  
25 recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis  
30 of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also

be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

#### **Example 30: Knock-Out Animals.**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene

of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & 5 Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered 10 to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, 15 muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the 20 transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The 25 engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; 30 genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and

Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

#### **Example 31: Production of an Antibody**

##### **Hybridoma Technology**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10

g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

*Isolation Of Antibody Fragments Directed polypeptide(s) of the invention  
From A Library Of scFvs*

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10<sup>9</sup> E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10<sup>8</sup> TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>13</sup> transducing units/ml (ampicillin-resistant clones).



Panning of the Library. Immuntubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

### **Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation**

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may

impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Purified polypeptides of the invention, or truncated forms thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$  M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of

SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer  
5 only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-  
10 arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell  
15 representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

20 Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to  
25 test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

### Example 33: T Cell Proliferation Assay

#### **Proliferation assay for Resting PBLs.**

30 A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of <sup>3</sup>H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control

mAb (B33.1) overnight at 4 °C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells ( $5 \times 10^4$ /well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 °C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20 °C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.4 microcuries of  $^3\text{H}$ -thymidine and cultured at 37 °C for 18-24 hr. Wells are harvested and incorporation of  $^3\text{H}$ -thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of  $^3\text{H}$ -thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using  $2 \times 10^4$  cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (\*), IFN  $\gamma$ , TNF  $\alpha$ , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of  $^3\text{H}$ -thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of  $^3\text{H}$ -thymidine is used as a measure of

proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(\*) The amount of the control cytokines IL-2, IFN , TNF and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

5

#### **Costimulation assay.**

A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using  $2 \times 10^4$  cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution,

30

therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of <sup>3</sup>H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of <sup>3</sup>H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

10

#### Costimulation assay: IFN $\gamma$ and IL-2 ELISA

The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using  $1 \times 10^5$  cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only(negative control), IL-2, IFN , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate. Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the

assay. ELISAs to test for IFN and IL-2 secretion are performed using kits purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

5           **Proliferation assay for preactivated-resting T cells.**

A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then  
10   cultured in the presence of low doses of IL-2 resemble effector T cells. These cells are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable  
15   to detect the effect of very low doses of an unknown growth factor, that would not be sufficient to induce proliferation on resting (naïve ) T cells.

The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in 10% FCS (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the  
20   presence of 2µg/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then washed in PBS and cultured in 10% FCS/RPMI in the presence of 5ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1%FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to  
25   determine the percentage of T cells (CD3 positive cells) present; this usually ranges between 93-97% depending on the donor. The assay is performed in a 96 well plate using  $2 \times 10^4$  cells/well in a final volume of 200µl. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60µl are added to 140µl of in 10% FCS/RPMI containing the cells. Control  
30   supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10ng/ml is

also used. After 24 hours of culture, each well is pulsed with 1  $\mu$ Ci of  $^3$ H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of  $^3$ H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

- 5        The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

10        **Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells**

- 15        Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

- 20        FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

- 30        **Effect on the production of cytokines.** Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune



response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ( $10^6$ /ml) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell  
5 cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g. R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion  
10 molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation.  
15 Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium  
20 azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that  
25 activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral  
30 blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque

gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively  
5 lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free  
10 medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a final concentration of 5  $\mu$ g/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA  
15 fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is  
20 performed as follows. Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h  
25 and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at  $2 \times 10^5$   
30 cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is

removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the  
5 reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H<sub>2</sub>O<sub>2</sub> produced by the macrophages, a standard curve of a H<sub>2</sub>O<sub>2</sub> solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies  
10 to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

### **Example 35: Biological Effects of Polypeptides of the Invention**

#### **Astrocyte and Neuronal Assays:**

15 Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1  
20 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron  
25 survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two  
30 responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to

induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

#### Fibroblast and endothelial cell assays

5 Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated  
10 for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays, the human lung fibroblasts are cultured at  
15 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to  
20 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth  
25 of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

#### Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of  
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic

projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP<sup>+</sup>) and released.

- 5 Subsequently, MPP<sup>+</sup> is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP<sup>+</sup> is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

- 10 It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

- Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of a polypeptide of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

- 30 Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons

would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells**

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2.5 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells**

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was

performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, VEGF<sub>165</sub> or a polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al. In Vitro Cell. Dev. Biol.* 30A:512-518 (1994).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect**

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida *et al.*, J. Biol. Chem. 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

### **Example 39: Stimulation of Endothelial Migration**

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

10 Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8  $\mu$ m (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate  
15 concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25  $\mu$ l of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber,  $2.5 \times 10^5$  cells suspended in 50  $\mu$ l M199 containing 1%  
20 FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO<sub>2</sub> to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by  
25 counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the  
30 invention.

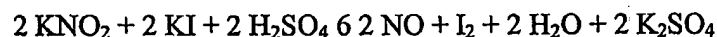


**Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells**

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:



The standard calibration curve is obtained by adding graded concentrations of  $\text{KNO}_2$  (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing KI and  $\text{H}_2\text{SO}_4$ . The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C. The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions.

S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per  $1 \times 10^6$  endothelial cells. All values reported are means of four to six measurements in each group (number of cell culture wells). See, Leak *et al. Biochem. and Biophys. Res. Comm.* 217:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to

test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5     **Example 41: Effect of Polypeptides of the Invention on Cord Formation in Angiogenesis**

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

10     CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 ml/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500  
15 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 mg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in  
20 triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

25     The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

30     **Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane**

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The

ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese quail (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of 16-day-old chick and 13-day-old quail embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cello tape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse**

*In vivo* angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the

mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 44: Rescue of Ischemia in Rabbit Lower Limb Model**

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol* 147:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita *et al.* *Am J. Pathol* 147:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al.* *Hum Gene Ther.* 4:749-758 (1993); Leclerc *et al.* *J. Clin. Invest.* 90: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1

min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number in the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

#### 15      **Example 45: Effect of Polypeptides of the Invention on Vasodilation**

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean  $\pm$  SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as  $p < 0.05$  vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### 30      **Example 46: Rat Ischemic Skin Flap Model**

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of

polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

Ischemic skin

5 Ischemic skin wounds

Normal wounds

The experimental protocol includes:

Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).

10 An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).

Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.

Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### 20 **Example 47: Peripheral Arterial Disease Model**

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

25 One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.

a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.

The ischemic muscle tissue is collected after ligation of the femoral  
30 artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

**Example 48: Ischemic Myocardial Disease Model**

A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 49: Rat Corneal Wound Healing Model**

This animal model shows the effect of a polypeptide of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm from the edge of the eye).

Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models**

##### ***Diabetic db+/db+ Mouse Model.***

To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These



homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

5 Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post  
10 treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

15 Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by  
20 treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit  
25 anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated  
30 by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a negative tissue control. Each specimen includes a section with omission of the primary

antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is  
5 considered significant.

### ***Steroid Impaired Rat Model***

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-  
10 Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *Am. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*,  
15 *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth*  
20 *Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that a polypeptide of the invention can accelerate the healing  
25 process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and  
30 are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad*

*libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

5        The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue  
10    punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

      Wounds are visually examined and photographed at a fixed distance at the day of  
15    wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

      The polypeptide of the invention is administered using at a range different doses,  
20    from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

      Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue  
25    cassettes between biopsy sponges for further processing.

      Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

      Wound closure is analyzed by measuring the area in the vertical and horizontal  
30    axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8).

The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch.

Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

5

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### 20      **Example 51: Lymphadema Animal Model**

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of a polypeptide of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing.

Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of  
5 dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main  
10 lymphatic vessels in this area are then electrically coagulated suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose  
15 tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying  
20 muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated  
25 places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb  
30 movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then  
5 dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca<sup>2+</sup> comparison.

10 Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee  
15 (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to  
20 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 52: Suppression of TNF alpha-induced adhesion molecule  
expression by a Polypeptide of the Invention**

25 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and  
30 endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and

extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

5 Tumor necrosis factor alpha (TNF- $\alpha$ ), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF- $\alpha$  induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- $\alpha$  treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>.

15 HUVECs are seeded in 96-well plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

20 Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90  $\mu$ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca<sup>++</sup> and Mg<sup>++</sup>) is added to each well. Plates are held at 4°C for 30 min.

25 Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10  $\mu$ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution



of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

- Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with
- 5 PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is
- 10 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [
- 15 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

- The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
- 20 invention.

**Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation**

- This assay is based on the ability of human CD34+ to proliferate in the
- 25 presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

- It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range
- 30 of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone

has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL-3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l SID (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60  $\mu$ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined

via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34<sup>+</sup> cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34<sup>+</sup> cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

**Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)**

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The

factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with  
5    in fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are  
plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the  
presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control,  
conditions under which little self-renewal but pronounced differentiation of the stem  
cells is to be expected. Gene products are tested with appropriate negative controls in  
10   the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent  
10% of the total assay volume. The plated cells are then allowed to grow by  
incubating in a low oxygen environment (5%  $\text{CO}_2$ , 7%  $\text{O}_2$ , and 88%  $\text{N}_2$ ) tissue  
culture incubator for 7 days. The number of proliferating cells within the wells is  
then quantitated by measuring thymidine incorporation into cellular DNA.  
15   Verification of the positive hits in the assay will require phenotypic characterization  
of the cells, which can be accomplished by scaling up of the culture system and using  
appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the  
activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or  
20   antagonists and fragments and variants thereof.

If a particular gene product is found to be a stimulator of hematopoietic  
progenitors, polynucleotides and polypeptides corresponding to the gene may be  
useful for the diagnosis and treatment of disorders affecting the immune system and  
hematopoiesis. Representative uses are described in the "Immune Activity" and  
25   "Infectious Disease" sections above, and elsewhere herein. The gene product may  
also be useful in the expansion of stem cells and committed progenitors of various  
blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest  
and/or agonists and/or antagonists thereof, may also be employed to inhibit the  
30   proliferation and differentiation of hematopoietic cells and therefore may be  
employed to protect bone marrow stem cells from chemotherapeutic agents during  
chemotherapy. This antiproliferative effect may allow administration of higher doses

of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

#### **Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation**

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for

AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls.

- 5 For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFα is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO<sub>2</sub> until day 5.

- 10 Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

- 15 On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 µl/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

- On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of  
20 Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

- 25 Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

- Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each  
30 assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or

smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

**Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells**

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in  
5 both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular  
10 endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are  
20 aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a  
25 concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtraAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with  
30 PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of



the ExtrAvidin-Alkaline Phosphatase in glycine buffer:  $1:5,000$  ( $10^0$ )  $> 10^{-0.5} > 10^{-1} > 10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNPN reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

#### **Example 57: Alamar Blue Endothelial Cells Proliferation Assay**

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The

plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

**Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction**

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml,

Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to  
5 wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration  
10 of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and  
15 compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or  
20 antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

25 The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both  
30 incorporated herein by reference in their entireties. Additionally, the specifications and sequence listings of U.S. Provisional Applications Serial Nos. 60/184,836 and 60/193,170 are all hereby incorporated by reference in their entirety.

**Table 3**  
(Gene No: 30 / Clone ID: HTPBW79)

|    | Res Position | I | II | III | IV | V | VI | VII | VIII  | IX    | X | XI | XII | XIII  | XIV  |
|----|--------------|---|----|-----|----|---|----|-----|-------|-------|---|----|-----|-------|------|
| 5  | Met 1        | . | .  | B   | B  | . | .  | .   | -0.37 | 0.07  | * | *  | .   | -0.30 | 0.86 |
|    | Arg 2        | . | .  | B   | B  | . | .  | .   | 0.02  | 0.43  | * | *  | .   | -0.60 | 0.59 |
|    | Thr 3        | . | .  | B   | B  | . | .  | .   | -0.40 | 0.40  | * | *  | .   | -0.30 | 0.74 |
|    | Leu 4        | A | A  | .   | .  | . | .  | .   | -0.82 | 0.66  | * | *  | .   | -0.60 | 0.61 |
| 10 | Phe 5        | A | A  | .   | .  | . | .  | .   | -0.72 | 0.73  | * | *  | .   | -0.60 | 0.26 |
|    | Asn 6        | A | A  | .   | .  | . | .  | .   | -0.93 | 1.64  | * | *  | .   | -0.60 | 0.19 |
|    | Leu 7        | A | A  | .   | .  | . | .  | .   | -1.63 | 1.84  | * | *  | .   | -0.60 | 0.19 |
|    | Leu 8        | A | A  | .   | .  | . | .  | .   | -2.13 | 1.66  | . | .  | .   | -0.60 | 0.22 |
|    | Trp 9        | A | A  | .   | .  | . | .  | .   | -1.91 | 1.56  | . | .  | .   | -0.60 | 0.11 |
| 15 | Leu 10       | A | A  | .   | .  | . | .  | .   | -1.88 | 1.66  | . | .  | .   | -0.60 | 0.14 |
|    | Ala 11       | A | A  | .   | .  | . | .  | .   | -2.18 | 1.54  | . | .  | .   | -0.60 | 0.09 |
|    | Leu 12       | A | A  | .   | .  | . | .  | .   | -1.58 | 1.24  | . | .  | .   | -0.60 | 0.11 |
|    | Ala 13       | A | A  | .   | .  | . | .  | .   | -1.62 | 0.76  | . | .  | .   | -0.60 | 0.21 |
|    | Cys 14       | . | A  | B   | .  | . | .  | .   | -1.37 | 0.71  | . | .  | .   | -0.60 | 0.16 |
| 20 | Ser 15       | . | A  | B   | .  | . | .  | .   | -0.87 | 0.71  | . | .  | .   | -0.60 | 0.26 |
|    | Pro 16       | . | .  | B   | B  | . | .  | .   | -0.59 | 0.51  | . | .  | .   | -0.60 | 0.37 |
|    | Val 17       | . | .  | B   | B  | . | .  | .   | -0.59 | 0.50  | . | .  | .   | -0.60 | 1.00 |
|    | His 18       | . | .  | B   | B  | . | .  | .   | -0.30 | 0.61  | * | .  | F   | -0.45 | 0.61 |
|    | Thr 19       | . | .  | B   | B  | . | .  | .   | 0.41  | 0.61  | * | .  | F   | -0.45 | 0.53 |
| 25 | Thr 20       | . | .  | B   | B  | . | .  | .   | 0.41  | 0.19  | . | .  | F   | 0.00  | 1.44 |
|    | Leu 21       | A | .  | .   | B  | . | .  | .   | 0.62  | -0.07 | . | .  | F   | 0.60  | 1.41 |
|    | Ser 22       | A | .  | .   | .  | . | T  | .   | 0.89  | -0.57 | . | *  | F   | 1.30  | 1.64 |
|    | Lys 23       | A | .  | .   | .  | . | T  | .   | 0.97  | -0.56 | . | .  | F   | 1.30  | 1.15 |
|    | Ser 24       | A | .  | .   | .  | . | T  | .   | 1.32  | -1.04 | . | .  | F   | 1.30  | 2.78 |
| 30 | Asp 25       | A | .  | .   | .  | . | T  | .   | 1.04  | -1.73 | . | .  | F   | 1.30  | 4.15 |
|    | Ala 26       | A | A  | .   | .  | . | .  | .   | 1.27  | -1.61 | . | .  | F   | 0.90  | 2.09 |
|    | Lys 27       | A | A  | .   | .  | . | .  | .   | 1.27  | -1.11 | * | .  | F   | 0.90  | 1.58 |
|    | Lys 28       | A | A  | .   | .  | . | .  | .   | 1.27  | -1.11 | * | *  | F   | 0.90  | 1.27 |
|    | Ala 29       | A | A  | .   | .  | . | .  | .   | 1.26  | -1.11 | * | .  | F   | 0.90  | 2.51 |
| 35 | Ala 30       | A | A  | .   | .  | . | .  | .   | 0.44  | -1.13 | * | .  | F   | 0.90  | 1.81 |
|    | Ser 31       | A | A  | .   | .  | . | .  | .   | 0.22  | -0.44 | * | .  | F   | 0.45  | 0.75 |
|    | Lys 32       | A | A  | .   | .  | . | .  | .   | 0.18  | 0.24  | . | .  | F   | -0.15 | 0.61 |
|    | Thr 33       | A | A  | .   | .  | . | .  | .   | 0.18  | -0.26 | . | .  | F   | 0.60  | 1.04 |
| 40 | Leu 34       | A | A  | .   | .  | . | .  | .   | 0.47  | -0.76 | . | .  | F   | 0.90  | 1.56 |
|    | Leu 35       | A | A  | .   | .  | . | .  | .   | 1.06  | -0.76 | . | .  | F   | 0.90  | 1.04 |
|    | Glu 36       | A | A  | .   | .  | . | .  | .   | 0.66  | -0.36 | . | .  | F   | 0.60  | 1.25 |
|    | Lys 37       | A | A  | .   | .  | . | .  | .   | 0.31  | -0.06 | . | .  | F   | 0.94  | 1.32 |
|    | Ser 38       | A | A  | .   | .  | . | .  | .   | 0.62  | -0.36 | . | *  | F   | 1.28  | 2.14 |
|    | Gln 39       | A | A  | .   | .  | . | .  | .   | 1.48  | -1.04 | . | *  | F   | 1.92  | 2.06 |
| 45 | Phe 40       | . | .  | .   | .  | T | T  | .   | 2.08  | -1.04 | . | .  | F   | 3.06  | 2.06 |
|    | Ser 41       | . | .  | .   | .  | T | T  | .   | 1.22  | -0.61 | . | .  | F   | 3.40  | 2.38 |
|    | Asp 42       | . | .  | .   | .  | T | T  | .   | 1.18  | -0.36 | . | *  | F   | 2.76  | 1.02 |
|    | Lys 43       | . | .  | .   | .  | . | T  | C   | 1.48  | -0.36 | . | *  | F   | 2.39  | 2.04 |
|    | Pro 44       | . | .  | .   | .  | . | .  | C   | 1.59  | -1.14 | . | *  | F   | 2.32  | 2.54 |
| 50 | Val 45       | . | .  | B   | .  | . | .  | .   | 1.94  | -1.53 | . | .  | F   | 1.95  | 2.98 |
|    | Gln 46       | . | .  | B   | .  | . | .  | .   | 1.43  | -1.10 | . | *  | F   | 1.78  | 1.47 |
|    | Asp 47       | . | .  | B   | .  | . | T  | .   | 0.58  | -0.41 | . | .  | F   | 1.70  | 0.79 |
|    | Arg 48       | . | .  | B   | .  | . | T  | .   | -0.32 | -0.20 | . | .  | F   | 1.53  | 0.79 |
|    | Gly 49       | . | .  | B   | .  | . | T  | .   | -0.42 | -0.20 | . | *  | F   | 1.36  | 0.34 |
| 55 | Leu 50       | . | .  | B   | .  | . | T  | .   | 0.43  | -0.11 | . | *  | .   | 1.04  | 0.29 |
|    | Val 51       | . | .  | B   | B  | . | .  | .   | -0.38 | -0.11 | . | *  | .   | 0.47  | 0.25 |
|    | Val 52       | . | .  | B   | B  | . | .  | .   | -0.33 | 0.57  | . | *  | .   | -0.60 | 0.21 |
|    | Thr 53       | . | .  | B   | B  | . | .  | .   | -1.03 | 0.14  | . | *  | F   | -0.15 | 0.50 |
|    | Asp 54       | A | .  | .   | B  | . | .  | .   | -0.69 | -0.04 | . | *  | F   | 0.45  | 0.68 |
| 60 | Leu 55       | A | A  | .   | .  | . | .  | .   | -0.18 | -0.69 | . | *  | F   | 0.90  | 1.59 |
|    | Lys 56       | A | A  | .   | .  | . | .  | .   | -0.18 | -0.94 | . | *  | F   | 0.90  | 1.48 |
|    | Ala 57       | A | A  | .   | .  | . | .  | .   | -0.18 | -0.79 | . | *  | F   | 0.75  | 0.66 |
|    | Glu 58       | A | A  | .   | B  | . | .  | .   | -0.68 | -0.14 | . | *  | F   | 0.45  | 0.59 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
| 5  | Ser | 59  | A | A | . | B | . | . | -0.68 | -0.14 | . | * | F | 0.45  | 0.24 |
|    | Val | 60  | A | A | . | B | . | . | 0.10  | -0.14 | . | * | . | 0.30  | 0.42 |
|    | Val | 61  | A | A | . | B | . | . | 0.17  | -0.14 | . | * | . | 0.30  | 0.33 |
|    | Leu | 62  | A | A | . | B | . | . | 0.46  | -0.14 | . | * | . | 0.30  | 0.48 |
|    | Glu | 63  | A | A | . | B | . | . | 0.21  | -0.14 | . | * | . | 0.30  | 0.87 |
|    | His | 64  | A | . | . | . | . | T | -0.16 | -0.03 | . | * | . | 0.85  | 1.83 |
|    | Arg | 65  | A | . | . | . | . | T | 0.40  | -0.10 | . | * | . | 0.85  | 1.19 |
|    | Ser | 66  | A | . | . | . | . | T | 0.67  | -0.40 | . | * | . | 0.70  | 0.92 |
| 10 | Tyr | 67  | A | . | . | . | . | T | 1.52  | 0.10  | . | * | . | 0.10  | 0.68 |
|    | Cys | 68  | A | A | . | . | . | . | 0.93  | -0.40 | . | * | . | 0.30  | 0.70 |
|    | Ser | 69  | A | A | . | . | . | . | 1.08  | 0.10  | . | * | . | -0.30 | 0.53 |
|    | Ala | 70  | A | A | . | . | . | . | 0.97  | -0.29 | . | * | . | 0.30  | 0.66 |
|    | Lys | 71  | A | A | . | . | . | . | 1.38  | -1.04 | . | * | F | 0.90  | 2.05 |
| 15 | Ala | 72  | A | A | . | . | . | . | 1.59  | -1.61 | . | * | F | 0.90  | 3.00 |
|    | Arg | 73  | A | A | . | . | . | . | 1.56  | -1.50 | . | * | F | 0.90  | 4.04 |
|    | Asp | 74  | A | A | . | . | . | . | 1.27  | -1.21 | . | * | F | 0.90  | 1.75 |
|    | Arg | 75  | A | A | . | . | . | . | 1.51  | -0.71 | . | * | . | 0.75  | 1.75 |
|    | His | 76  | . | A | B | . | . | . | 1.47  | -0.79 | . | * | . | 0.60  | 0.88 |
| 20 | Phe | 77  | . | A | B | . | . | . | 1.20  | -0.79 | . | * | . | 0.60  | 0.88 |
|    | Ala | 78  | . | A | B | . | . | . | 0.28  | -0.14 | . | * | . | 0.30  | 0.33 |
|    | Gly | 79  | . | . | B | B | . | . | -0.07 | 0.54  | . | . | . | -0.60 | 0.20 |
|    | Asp | 80  | . | . | . | B | T | . | -0.42 | 0.47  | * | . | . | -0.20 | 0.23 |
|    | Val | 81  | . | . | B | B | . | . | -1.24 | 0.44  | * | * | . | -0.60 | 0.36 |
| 25 | Leu | 82  | . | . | B | B | . | . | -0.86 | 0.59  | . | * | . | -0.60 | 0.27 |
|    | Gly | 83  | . | . | B | B | . | . | -0.48 | 0.64  | . | . | . | -0.60 | 0.23 |
|    | Tyr | 84  | . | . | B | B | . | . | -0.42 | 1.07  | . | . | . | -0.60 | 0.49 |
|    | Val | 85  | . | . | B | B | . | . | -0.42 | 1.34  | . | . | . | -0.60 | 0.62 |
|    | Thr | 86  | . | . | B | B | . | . | 0.13  | 1.06  | . | . | . | -0.45 | 1.01 |
| 30 | Pro | 87  | . | . | B | B | . | . | 0.91  | 1.01  | . | . | . | -0.45 | 0.86 |
|    | Trp | 88  | . | . | . | . | T | . | 0.91  | 0.76  | . | . | F | 0.30  | 1.58 |
|    | Asn | 89  | . | . | . | . | . | T | 0.91  | 0.54  | . | . | F | 0.30  | 1.08 |
|    | Ser | 90  | . | . | . | . | . | T | 1.77  | 0.81  | * | . | . | 0.15  | 1.10 |
|    | His | 91  | . | . | . | . | . | T | 1.22  | 0.39  | . | . | . | 0.45  | 1.74 |
| 35 | Gly | 92  | . | . | . | . | T | T | 1.12  | 0.11  | * | . | . | 0.50  | 0.80 |
|    | Tyr | 93  | . | . | . | B | T | . | 1.46  | 0.20  | * | . | . | 0.10  | 0.87 |
|    | Asp | 94  | . | . | B | B | . | . | 0.60  | -0.19 | * | . | . | 0.45  | 1.27 |
|    | Val | 95  | . | . | B | B | . | . | 0.20  | -0.04 | * | . | . | 0.30  | 0.95 |
|    | Thr | 96  | . | . | B | B | . | . | -0.11 | 0.31  | * | . | . | -0.30 | 0.53 |
| 40 | Lys | 97  | . | . | B | B | . | . | -0.07 | -0.01 | * | . | F | 0.45  | 0.31 |
|    | Val | 98  | . | . | B | B | . | . | 0.22  | 0.37  | * | . | F | -0.15 | 0.56 |
|    | Phe | 99  | . | . | B | B | . | . | -0.48 | -0.27 | * | . | F | 0.45  | 0.78 |
|    | Gly | 100 | . | . | . | B | T | . | 0.07  | 0.03  | * | . | F | 0.25  | 0.34 |
|    | Ser | 101 | . | . | B | B | . | . | 0.38  | 0.51  | * | . | F | -0.45 | 0.66 |
| 45 | Lys | 102 | . | . | B | B | . | . | -0.56 | 0.27  | * | . | F | 0.00  | 1.32 |
|    | Phe | 103 | . | . | . | B | T | . | 0.00  | 0.17  | . | . | F | 0.25  | 0.93 |
|    | Thr | 104 | . | . | B | B | . | . | 0.49  | 0.13  | * | . | F | -0.15 | 0.93 |
|    | Gln | 105 | . | . | B | B | . | . | -0.02 | 0.17  | . | . | F | -0.15 | 0.72 |
|    | Ile | 106 | . | . | B | B | . | . | -0.01 | 0.81  | . | . | F | -0.45 | 0.62 |
| 50 | Ser | 107 | . | . | B | B | . | . | -0.87 | 0.94  | * | . | F | -0.45 | 0.45 |
|    | Pro | 108 | . | . | B | B | . | . | -0.17 | 1.14  | * | . | . | -0.60 | 0.21 |
|    | Val | 109 | . | A | B | B | . | . | -0.67 | 1.14  | . | * | . | -0.60 | 0.53 |
|    | Trp | 110 | . | A | B | B | . | . | -0.62 | 1.14  | * | . | . | -0.60 | 0.33 |
|    | Leu | 111 | . | A | B | B | . | . | 0.38  | 0.76  | * | * | . | -0.30 | 0.42 |
| 55 | Gln | 112 | . | A | B | B | . | . | 0.79  | 0.33  | * | * | . | 0.45  | 1.11 |
|    | Leu | 113 | . | A | B | B | . | . | 0.66  | -0.31 | * | * | . | 1.35  | 2.07 |
|    | Lys | 114 | . | A | . | B | . | . | 1.62  | -0.80 | * | * | F | 2.30  | 2.49 |
|    | Arg | 115 | . | . | . | . | . | T | 1.91  | -1.49 | * | * | F | 3.00  | 2.81 |
|    | Arg | 116 | . | . | . | . | . | T | 2.12  | -1.89 | * | * | F | 2.70  | 5.90 |
| 60 | Gly | 117 | . | . | . | . | . | T | 1.42  | -1.96 | * | * | F | 2.40  | 2.92 |
|    | Arg | 118 | . | . | . | . | . | T | 2.23  | -1.17 | * | * | F | 2.10  | 1.29 |
|    | Glu | 119 | A | A | B | . | . | . | 1.33  | -1.17 | * | * | . | 1.05  | 1.14 |
|    | Met | 120 | A | A | . | B | . | . | 0.91  | -0.53 | * | * | . | 0.60  | 0.86 |
|    | Phe | 121 | A | A | . | B | . | . | 0.46  | -0.47 | . | * | . | 0.30  | 0.63 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | Glu | 122 | A | A | . | B | . | . | -0.01 | -0.04 | . | * | . | 0.30  | 0.36 |
|    | Val | 123 | A | A | . | B | . | . | -0.16 | 0.64  | . | * | . | -0.60 | 0.30 |
|    | Thr | 124 | A | A | . | B | . | . | -0.16 | 0.53  | . | . | . | -0.60 | 0.47 |
| 5  | Gly | 125 | A | A | . | B | . | . | -0.41 | -0.26 | . | * | . | 0.30  | 0.46 |
|    | Leu | 126 | A | . | . | B | . | . | 0.29  | 0.39  | . | * | . | -0.30 | 0.46 |
|    | His | 127 | A | . | . | B | . | . | 0.29  | -0.26 | . | . | . | 0.30  | 0.53 |
|    | Asp | 128 | A | . | . | . | . | . | 0.80  | -0.34 | * | . | . | 0.50  | 0.92 |
|    | Val | 129 | A | . | . | . | . | . | 0.82  | -0.34 | * | . | F | 0.80  | 1.11 |
| 10 | Asp | 130 | A | . | . | . | . | T | 0.57  | -0.11 | * | . | F | 0.85  | 0.86 |
|    | Gln | 131 | A | . | . | . | . | T | 1.49  | 0.00  | * | . | F | 0.25  | 0.51 |
|    | Gly | 132 | A | . | . | . | . | T | 0.93  | 0.00  | * | . | F | 0.40  | 1.34 |
|    | Trp | 133 | A | . | . | . | . | T | 0.08  | -0.14 | * | . | . | 0.70  | 0.81 |
|    | Met | 134 | A | A | . | . | . | . | 1.04  | 0.50  | * | . | . | -0.60 | 0.35 |
|    | Arg | 135 | A | A | . | . | . | . | 1.09  | 0.10  | * | . | . | -0.30 | 0.69 |
| 15 | Ala | 136 | A | A | . | . | . | . | 1.06  | -0.33 | * | . | . | 0.45  | 1.30 |
|    | Val | 137 | A | A | . | . | . | . | 0.81  | -0.74 | * | * | . | 0.75  | 1.79 |
|    | Arg | 138 | A | A | . | . | . | . | 1.14  | -0.86 | * | * | . | 0.60  | 0.93 |
|    | Lys | 139 | A | A | . | . | . | . | 1.40  | -0.86 | * | . | F | 0.90  | 1.83 |
| 20 | His | 140 | A | A | . | . | . | . | 0.48  | -0.93 | * | . | F | 0.90  | 2.44 |
|    | Ala | 141 | A | A | . | . | . | . | 1.03  | -0.89 | * | * | F | 0.90  | 1.03 |
|    | Lys | 142 | A | A | . | . | . | . | 1.00  | -0.39 | * | * | F | 0.45  | 0.70 |
|    | Gly | 143 | . | A | B | . | . | . | 0.03  | 0.30  | * | . | . | -0.30 | 0.36 |
|    | Leu | 144 | . | A | B | . | . | . | -0.22 | 0.44  | * | . | . | -0.60 | 0.26 |
| 25 | His | 145 | . | A | B | . | . | . | -0.08 | 0.37  | * | * | . | -0.30 | 0.20 |
|    | Ile | 146 | . | A | B | . | . | . | -0.30 | 0.37  | * | * | . | -0.30 | 0.41 |
|    | Val | 147 | . | A | B | . | . | . | -1.16 | 0.63  | * | * | . | -0.60 | 0.41 |
|    | Pro | 148 | . | A | B | . | . | . | -1.51 | 0.63  | * | * | . | -0.60 | 0.25 |
|    | Arg | 149 | . | A | B | . | . | . | -0.70 | 0.91  | * | * | . | -0.60 | 0.30 |
| 30 | Leu | 150 | . | A | B | . | . | . | -0.67 | 0.23  | * | * | . | -0.30 | 0.71 |
|    | Leu | 151 | . | A | B | . | . | . | -0.07 | -0.41 | * | * | . | 0.30  | 0.76 |
|    | Phe | 152 | . | A | B | . | . | . | 0.48  | 0.07  | * | . | . | -0.30 | 0.41 |
|    | Glu | 153 | A | A | . | . | . | . | 0.44  | 0.56  | . | * | . | -0.60 | 0.72 |
|    | Asp | 154 | . | A | . | . | . | T | 0.33  | 0.63  | . | * | . | -0.05 | 1.37 |
| 35 | Trp | 155 | . | A | . | . | . | T | 1.14  | -0.06 | . | . | . | 1.19  | 2.63 |
|    | Thr | 156 | A | A | . | . | . | . | 1.26  | -0.84 | * | * | . | 1.43  | 2.54 |
|    | Tyr | 157 | . | . | . | . | . | T | 2.07  | -0.06 | * | . | . | 2.27  | 1.32 |
|    | Asp | 158 | . | . | . | . | . | T | 2.07  | -0.06 | * | . | F | 2.76  | 2.45 |
|    | Asp | 159 | . | . | . | . | . | T | 1.21  | -0.57 | * | . | F | 3.40  | 2.73 |
| 40 | Phe | 160 | . | . | . | . | . | T | 0.69  | -0.41 | * | * | F | 2.76  | 1.29 |
|    | Arg | 161 | . | . | B | B | . | . | 1.00  | -0.49 | * | * | F | 1.47  | 0.64 |
|    | Asn | 162 | . | . | B | B | . | . | 0.94  | -0.49 | * | * | . | 0.98  | 0.64 |
|    | Val | 163 | . | . | . | B | . | C | 0.94  | -0.10 | * | * | . | 0.84  | 0.99 |
|    | Leu | 164 | . | . | . | B | . | C | 0.94  | -0.89 | * | * | F | 0.95  | 0.87 |
| 45 | Asp | 165 | A | . | . | . | . | T | 1.64  | -0.89 | * | * | F | 1.15  | 0.91 |
|    | Ser | 166 | A | . | . | . | . | T | 0.64  | -1.29 | * | * | F | 1.30  | 2.12 |
|    | Glu | 167 | A | . | . | . | . | T | 0.64  | -1.24 | * | . | F | 1.30  | 1.80 |
|    | Asp | 168 | A | . | . | . | . | T | 1.50  | -1.93 | * | . | F | 1.30  | 1.87 |
|    | Glu | 169 | A | A | . | . | . | . | 1.50  | -1.93 | . | * | F | 0.90  | 2.41 |
| 50 | Ile | 170 | A | A | . | . | . | . | 1.20  | -1.63 | * | . | F | 0.90  | 1.15 |
|    | Glu | 171 | A | A | . | . | . | . | 1.54  | -1.24 | * | . | F | 0.75  | 0.92 |
|    | Glu | 172 | A | A | . | . | . | . | 1.23  | -1.24 | * | . | F | 0.90  | 1.07 |
|    | Leu | 173 | A | A | . | . | . | . | 0.38  | -0.76 | * | . | F | 0.90  | 2.19 |
|    | Ser | 174 | A | . | . | B | . | . | -0.48 | -0.80 | * | . | F | 0.75  | 0.94 |
| 55 | Lys | 175 | A | . | . | B | . | . | 0.41  | -0.16 | * | . | F | 0.45  | 0.40 |
|    | Thr | 176 | A | . | . | B | . | . | -0.44 | 0.24  | * | . | F | -0.15 | 0.85 |
|    | Val | 177 | A | . | . | B | . | . | -1.03 | 0.20  | * | . | . | -0.30 | 0.47 |
|    | Val | 178 | A | . | . | B | . | . | -0.18 | 0.31  | * | . | . | -0.30 | 0.24 |
|    | Gln | 179 | A | . | . | B | . | . | 0.12  | 0.31  | * | . | . | -0.30 | 0.33 |
| 60 | Val | 180 | A | . | . | B | . | . | 0.08  | 0.23  | * | . | . | -0.30 | 0.71 |
|    | Ala | 181 | . | . | B | B | . | . | 0.36  | -0.01 | . | . | . | 0.45  | 1.66 |
|    | Lys | 182 | A | . | . | B | . | . | 0.51  | -0.16 | . | . | F | 0.70  | 1.30 |
|    | Asn | 183 | . | . | B | . | . | . | 1.37  | 0.23  | . | . | F | 0.40  | 1.52 |
|    | Gln | 184 | . | . | B | . | . | . | 1.02  | -0.41 | . | . | F | 1.10  | 2.51 |

|    |     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | His | 185 | . | . | . | . | . | T | C | 1.18  | -0.49 | . | . | F | 1.60  | 1.24 |
|    | Phe | 186 | . | . | . | . | T | T | . | 0.91  | 0.30  | . | . | . | 1.00  | 0.67 |
|    | Asp | 187 | . | . | B | . | . | T | . | 0.01  | 0.54  | . | . | . | 0.20  | 0.29 |
| 5  | Gly | 188 | . | . | B | . | . | T | . | 0.01  | 0.79  | * | . | . | 0.10  | 0.16 |
|    | Phe | 189 | . | . | B | B | . | . | . | -0.84 | 0.29  | * | . | . | -0.10 | 0.31 |
|    | Val | 190 | . | . | B | B | . | . | . | -1.10 | 0.14  | * | . | . | -0.20 | 0.14 |
|    | Val | 191 | . | . | B | B | . | . | . | -0.40 | 1.06  | * | . | . | -0.60 | 0.15 |
|    | Glu | 192 | A | . | . | B | . | . | . | -0.40 | 1.03  | * | . | . | -0.60 | 0.27 |
|    | Val | 193 | A | . | . | B | . | . | . | -0.87 | 0.64  | * | . | . | -0.60 | 0.64 |
| 10 | Trp | 194 | A | . | . | B | . | . | . | -0.98 | 0.69  | * | . | . | -0.60 | 0.71 |
|    | Asn | 195 | A | . | . | B | . | . | . | -0.42 | 0.73  | * | . | . | -0.60 | 0.34 |
|    | Gln | 196 | A | . | . | B | . | . | . | 0.43  | 1.11  | . | . | . | -0.60 | 0.61 |
|    | Leu | 197 | A | . | . | B | . | . | . | 0.48  | 0.87  | * | . | F | -0.30 | 1.01 |
|    | Leu | 198 | A | . | . | B | . | . | . | 1.44  | -0.04 | . | . | F | 0.78  | 1.25 |
| 15 | Ser | 199 | . | . | . | B | . | . | C | 0.88  | -0.44 | . | * | F | 1.16  | 1.42 |
|    | Gln | 200 | . | . | . | B | T | . | . | 0.57  | -0.20 | . | . | F | 1.54  | 1.28 |
|    | Lys | 201 | . | . | B | B | . | . | . | 0.57  | -0.40 | . | * | F | 1.32  | 2.23 |
|    | Arg | 202 | . | . | B | B | . | . | . | 1.38  | -1.09 | * | * | F | 1.80  | 2.78 |
|    | Val | 203 | . | . | B | B | . | . | . | 1.38  | -1.07 | * | . | F | 1.62  | 2.78 |
| 20 | Thr | 204 | . | . | B | B | . | . | . | 1.33  | -0.79 | * | * | F | 1.44  | 1.15 |
|    | Asp | 205 | . | . | B | . | . | T | . | 0.73  | -0.36 | * | * | F | 1.21  | 0.58 |
|    | Gln | 206 | A | . | . | . | . | T | . | -0.01 | 0.26  | * | . | . | 0.28  | 0.77 |
|    | Leu | 207 | A | . | . | . | . | T | . | -0.43 | 0.40  | * | * | . | -0.20 | 0.46 |
|    | Gly | 208 | A | . | . | . | . | T | . | 0.39  | 0.40  | * | . | . | -0.20 | 0.40 |
| 25 | Met | 209 | A | A | . | . | . | . | . | 0.74  | 0.90  | . | . | . | -0.60 | 0.31 |
|    | Phe | 210 | A | A | . | . | . | . | . | 0.74  | 0.50  | . | . | . | -0.60 | 0.76 |
|    | Thr | 211 | A | A | . | . | . | . | . | 0.04  | -0.19 | * | . | . | 0.45  | 1.34 |
|    | His | 212 | A | A | . | . | . | . | . | 0.86  | 0.17  | . | . | . | -0.15 | 1.17 |
| 30 | Lys | 213 | A | A | . | . | . | . | . | 1.20  | -0.44 | * | . | F | 0.60  | 2.34 |
|    | Glu | 214 | A | A | . | . | . | . | . | 0.99  | -0.83 | * | . | F | 0.90  | 2.81 |
|    | Phe | 215 | A | A | . | . | . | . | . | 1.10  | -0.63 | * | . | F | 0.90  | 1.70 |
|    | Glu | 216 | A | A | . | . | . | . | . | 1.20  | -0.63 | * | . | F | 0.75  | 0.86 |
|    | Gln | 217 | A | A | . | . | . | . | . | 0.38  | -0.20 | * | . | . | 0.30  | 0.77 |
| 35 | Leu | 218 | A | A | . | . | . | . | . | -0.48 | 0.44  | * | . | . | -0.60 | 0.66 |
|    | Ala | 219 | A | A | . | . | . | . | . | -0.48 | 0.34  | * | . | . | -0.30 | 0.31 |
|    | Pro | 220 | A | . | . | . | . | . | . | -0.12 | 0.34  | * | . | . | -0.10 | 0.30 |
|    | Val | 221 | A | . | . | . | . | . | . | -0.82 | 0.37  | * | . | . | -0.10 | 0.36 |
|    | Leu | 222 | A | . | . | . | . | . | . | -1.12 | 0.47  | . | . | . | -0.40 | 0.31 |
| 40 | Asp | 223 | A | . | . | . | . | T | . | -1.12 | 0.36  | . | . | . | 0.10  | 0.27 |
|    | Gly | 224 | . | . | B | . | . | T | . | -1.13 | 0.61  | . | . | . | -0.20 | 0.30 |
|    | Phe | 225 | . | . | B | . | . | T | . | -1.23 | 0.59  | . | . | . | -0.20 | 0.36 |
|    | Ser | 226 | . | . | B | . | . | T | . | -0.62 | 0.39  | . | . | . | 0.10  | 0.31 |
|    | Leu | 227 | . | . | B | . | . | . | . | 0.19  | 1.14  | . | . | . | -0.40 | 0.49 |
| 45 | Met | 228 | . | . | B | . | . | . | . | -0.06 | 0.71  | . | . | . | -0.40 | 0.95 |
|    | Thr | 229 | . | . | B | . | . | T | . | -0.01 | 0.69  | . | . | . | -0.05 | 1.11 |
|    | Tyr | 230 | . | . | . | . | T | T | . | 0.38  | 0.69  | . | . | . | 0.35  | 1.80 |
|    | Asp | 231 | . | . | . | . | T | T | . | 0.09  | 0.49  | . | . | . | 0.35  | 2.62 |
|    | Tyr | 232 | . | . | . | . | T | T | . | 0.87  | 0.37  | . | . | . | 0.65  | 1.84 |
| 50 | Ser | 233 | . | . | B | . | . | . | . | 1.47  | 0.39  | . | . | . | 0.05  | 1.59 |
|    | Thr | 234 | . | . | B | . | . | . | . | 1.57  | 0.03  | . | . | . | 0.05  | 1.65 |
|    | Ala | 235 | . | . | B | . | . | . | . | 1.47  | 0.46  | . | . | . | -0.25 | 1.63 |
|    | His | 236 | . | . | B | . | . | . | . | 1.26  | 0.13  | . | . | F | 0.20  | 1.21 |
|    | Gln | 237 | . | . | . | . | . | . | C | 1.50  | 0.17  | . | . | F | 0.40  | 1.29 |
| 55 | Pro | 238 | . | . | . | . | . | . | C | 1.21  | 0.09  | . | . | F | 0.40  | 2.06 |
|    | Gly | 239 | . | . | . | . | . | T | C | 1.31  | 0.09  | . | . | F | 0.60  | 1.53 |
|    | Pro | 240 | . | . | . | . | T | T | . | 1.09  | 0.01  | . | . | F | 0.80  | 1.36 |
|    | Asn | 241 | . | . | . | . | . | T | C | 0.82  | 0.30  | . | * | F | 0.45  | 0.73 |
|    | Ala | 242 | . | . | . | . | . | T | C | 0.53  | 0.26  | . | . | F | 0.45  | 0.98 |
|    | Pro | 243 | . | . | B | . | . | . | . | -0.11 | 0.74  | * | . | . | -0.40 | 0.67 |
| 60 | Leu | 244 | . | . | B | B | . | . | . | 0.34  | 0.96  | * | . | . | -0.60 | 0.31 |
|    | Ser | 245 | . | . | B | B | . | . | . | -0.03 | 0.56  | * | . | . | -0.60 | 0.60 |
|    | Trp | 246 | . | . | B | B | . | . | . | -0.70 | 0.56  | * | * | . | -0.60 | 0.39 |
|    | Val | 247 | . | . | B | B | . | . | . | -0.97 | 0.70  | * | * | . | -0.60 | 0.25 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
| 5  | Arg | 248 | . | . | B | B | . | . | -0.76 | 0.66  | * | * | . | -0.60 | 0.14 |
|    | Ala | 249 | . | . | B | B | . | . | -0.80 | 0.67  | * | * | . | -0.60 | 0.23 |
|    | Cys | 250 | . | . | B | B | . | . | -1.31 | 0.40  | * | * | . | -0.60 | 0.23 |
|    | Val | 251 | . | . | B | B | . | . | -1.02 | 0.44  | * | * | . | -0.60 | 0.10 |
|    | Gln | 252 | . | . | B | B | . | . | -0.38 | 0.44  | * | * | . | -0.60 | 0.16 |
|    | Val | 253 | . | . | B | B | . | . | -0.44 | 0.37  | * | * | . | 0.04  | 0.47 |
|    | Leu | 254 | . | . | B | B | . | . | -0.16 | -0.20 | . | * | . | 1.13  | 1.25 |
|    | Asp | 255 | . | . | B | . | . | T | 0.56  | -0.46 | . | * | F | 1.87  | 0.97 |
| 10 | Pro | 256 | . | . | . | . | T | T | 1.12  | -0.86 | . | * | F | 3.06  | 2.62 |
|    | Lys | 257 | . | . | . | . | T | T | 1.23  | -0.59 | . | * | F | 3.40  | 3.34 |
|    | Ser | 258 | A | . | . | . | . | T | 1.79  | -1.27 | . | * | F | 2.66  | 3.91 |
|    | Lys | 259 | A | . | . | . | . | . | 2.64  | -0.89 | . | * | F | 2.12  | 3.39 |
|    | Trp | 260 | A | . | . | . | . | T | 1.76  | -1.31 | . | * | F | 1.98  | 3.39 |
| 15 | Arg | 261 | A | . | . | . | . | T | 1.16  | -0.63 | . | * | F | 1.64  | 1.77 |
|    | Ser | 262 | . | . | B | . | . | T | 0.30  | -0.33 | . | * | F | 0.85  | 0.73 |
|    | Lys | 263 | . | . | B | . | . | T | 0.26  | 0.36  | . | * | F | 0.25  | 0.57 |
|    | Ile | 264 | . | . | B | B | . | . | -0.60 | -0.13 | . | * | . | 0.30  | 0.29 |
|    | Leu | 265 | . | . | B | B | . | . | -0.31 | 0.56  | . | * | . | -0.60 | 0.18 |
| 20 | Leu | 266 | . | . | B | B | . | . | -1.12 | 0.57  | . | * | . | -0.60 | 0.14 |
|    | Gly | 267 | . | . | B | B | . | . | -1.07 | 1.36  | . | * | . | -0.60 | 0.18 |
|    | Leu | 268 | . | . | B | . | . | . | -1.46 | 1.43  | . | * | . | -0.40 | 0.34 |
|    | Asn | 269 | . | . | B | . | . | . | -1.17 | 1.17  | . | * | . | -0.40 | 0.40 |
|    | Phe | 270 | . | . | B | . | . | . | -0.36 | 1.10  | . | . | . | -0.40 | 0.40 |
| 25 | Tyr | 271 | . | . | B | . | . | . | 0.21  | 0.67  | . | * | . | -0.40 | 0.82 |
|    | Gly | 272 | . | . | B | . | . | T | -0.03 | 0.74  | . | . | . | -0.20 | 0.80 |
|    | Met | 273 | . | . | B | . | . | T | 0.47  | 0.84  | . | . | . | -0.20 | 0.93 |
|    | Asp | 274 | . | . | B | . | . | T | 0.17  | 0.54  | . | . | . | -0.20 | 0.86 |
|    | Tyr | 275 | A | . | . | . | . | T | 0.91  | 0.17  | . | . | . | 0.25  | 1.16 |
| 30 | Ala | 276 | A | . | . | . | . | . | 1.16  | -0.26 | . | . | . | 0.65  | 2.34 |
|    | Thr | 277 | A | . | . | . | . | . | 0.91  | -0.87 | . | * | F | 1.10  | 2.34 |
|    | Ser | 278 | A | . | . | . | . | T | 1.62  | -0.37 | * | . | F | 1.00  | 1.51 |
|    | Lys | 279 | A | . | . | . | . | T | 1.62  | -1.13 | . | . | F | 1.30  | 2.93 |
|    | Asp | 280 | A | . | . | . | . | T | 1.66  | -1.63 | * | * | F | 1.30  | 3.52 |
| 35 | Ala | 281 | A | . | . | . | . | T | 1.39  | -1.69 | . | . | F | 1.30  | 4.06 |
|    | Arg | 282 | . | . | B | . | . | . | 0.84  | -1.43 | . | . | F | 1.10  | 1.51 |
|    | Glu | 283 | . | . | B | B | . | . | 0.80  | -0.79 | * | . | F | 0.75  | 0.67 |
|    | Pro | 284 | . | . | B | B | . | . | 0.17  | -0.36 | * | . | F | 0.45  | 0.66 |
|    | Val | 285 | . | . | B | B | . | . | 0.28  | -0.36 | * | * | . | 0.30  | 0.34 |
| 40 | Val | 286 | . | . | B | B | . | . | 0.62  | -0.36 | * | * | . | 0.30  | 0.38 |
|    | Gly | 287 | . | . | B | . | . | T | -0.38 | 0.40  | * | . | . | -0.20 | 0.39 |
|    | Ala | 288 | . | . | B | . | . | T | -0.38 | 0.66  | . | . | . | -0.20 | 0.37 |
|    | Arg | 289 | . | . | B | . | . | T | -0.48 | 0.41  | * | . | . | -0.20 | 0.85 |
|    | Tyr | 290 | . | . | B | . | . | T | -0.43 | 0.26  | * | * | . | 0.25  | 1.25 |
| 45 | Ile | 291 | . | A | B | B | . | . | 0.47  | 0.51  | * | * | . | -0.45 | 1.02 |
|    | Gln | 292 | . | A | B | B | . | . | 0.81  | 0.01  | * | . | . | -0.15 | 1.04 |
|    | Thr | 293 | . | A | B | B | . | . | 1.37  | 0.01  | * | * | F | 0.00  | 1.11 |
|    | Leu | 294 | . | A | B | B | . | . | 1.37  | -0.24 | * | . | F | 0.90  | 2.15 |
|    | Lys | 295 | . | A | . | B | . | T | 1.40  | -0.93 | . | * | F | 1.90  | 2.43 |
| 50 | Asp | 296 | . | A | . | . | . | T | 2.40  | -0.90 | . | * | F | 2.20  | 2.60 |
|    | His | 297 | . | A | . | . | . | . | 1.80  | -1.39 | . | * | F | 2.30  | 6.18 |
|    | Arg | 298 | . | . | . | . | . | T | 1.26  | -1.46 | . | * | F | 3.00  | 3.06 |
|    | Pro | 299 | . | . | B | . | . | T | 1.78  | -0.81 | . | * | F | 2.50  | 1.36 |
|    | Arg | 300 | . | . | B | . | . | T | 1.73  | 0.10  | . | * | . | 1.15  | 1.05 |
| 55 | Met | 301 | . | . | B | . | . | T | 1.43  | -0.40 | . | * | . | 1.30  | 0.90 |
|    | Val | 302 | . | . | B | . | . | . | 1.47  | -0.01 | . | * | . | 0.80  | 0.78 |
|    | Trp | 303 | . | . | B | . | . | T | 0.97  | -0.04 | . | * | . | 0.70  | 0.69 |
|    | Asp | 304 | . | . | . | . | . | T | 0.88  | 0.39  | . | * | F | 0.45  | 0.89 |
|    | Ser | 305 | . | . | . | . | . | T | 0.77  | 0.16  | . | * | F | 0.60  | 1.60 |
| 60 | Gln | 306 | . | . | . | . | . | T | 1.33  | -0.49 | . | . | F | 1.20  | 2.64 |
|    | Xxx | 307 | . | A | . | . | . | . | 1.49  | -0.90 | . | . | F | 1.10  | 2.15 |
|    | Ser | 308 | A | A | . | . | . | . | 1.08  | -0.11 | . | . | F | 0.60  | 1.39 |
|    | Glu | 309 | A | A | . | . | . | . | 1.08  | 0.29  | . | . | F | -0.15 | 0.69 |
|    | His | 310 | A | A | . | . | . | . | 1.13  | -0.11 | . | . | . | 0.30  | 0.94 |



|    |     |     |   |   |   |   |   |   |   |       |       |   |   |   |        |      |
|----|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|--------|------|
|    | Phe | 311 | A | A | . | . | . | . | . | 1.18  | 0.21  | . | . | . | -0.15  | 1.10 |
|    | Phe | 312 | A | A | . | . | . | . | . | 1.61  | -0.17 | . | . | . | 0.45   | 1.27 |
|    | Glu | 313 | A | A | . | . | . | . | . | 1.61  | -0.17 | . | . | . | 0.79   | 1.87 |
|    | Tyr | 314 | A | A | . | . | . | . | . | 1.72  | -0.29 | . | . | . | 1.13   | 2.89 |
| 5  | Lys | 315 | A | A | . | . | . | . | . | 1.46  | -1.07 | . | . | . | F 1.92 | 6.53 |
|    | Lys | 316 | . | A | . | . | . | T | . | 1.81  | -1.47 | . | . | . | F 2.66 | 5.05 |
|    | Ser | 317 | . | . | . | . | . | T | T | 2.62  | -1.04 | * | . | . | F 3.40 | 3.19 |
|    | Arg | 318 | . | . | . | . | . | T | T | 2.59  | -1.80 | * | . | . | F 3.06 | 3.13 |
|    | Ser | 319 | . | . | . | . | . | T | T | 1.98  | -1.30 | * | . | . | F 2.72 | 2.13 |
| 10 | Gly | 320 | . | . | . | . | . | T | T | 1.08  | -0.66 | * | . | . | F 2.38 | 1.18 |
|    | Arg | 321 | . | . | . | B | B | . | . | 0.33  | -0.40 | . | . | . | F 0.79 | 0.45 |
|    | His | 322 | . | . | . | B | B | . | . | 0.39  | 0.39  | * | . | . | -0.30  | 0.29 |
|    | Val | 323 | . | . | . | B | B | . | . | 0.07  | 0.76  | * | . | . | -0.60  | 0.46 |
|    | Val | 324 | . | . | . | B | B | . | . | 0.06  | 0.76  | . | . | . | -0.60  | 0.36 |
| 15 | Phe | 325 | . | . | . | B | B | . | . | -0.41 | 1.24  | . | * | . | -0.60  | 0.38 |
|    | Tyr | 326 | . | . | . | B | B | . | . | -0.48 | 1.43  | . | * | . | -0.60  | 0.42 |
|    | Pro | 327 | . | . | . | B | B | . | . | -0.74 | 0.79  | . | . | F | -0.30  | 1.14 |
|    | Thr | 328 | . | A | . | . | . | T | . | -0.70 | 0.53  | . | . | F | 0.10   | 1.77 |
| 20 | Leu | 329 | A | A | . | . | . | . | . | 0.16  | 0.43  | * | . | F | -0.45  | 0.93 |
|    | Lys | 330 | A | A | . | . | . | . | . | 0.00  | 0.07  | . | * | F | 0.00   | 1.04 |
|    | Ser | 331 | A | A | . | . | . | . | . | 0.36  | 0.29  | . | * | F | -0.15  | 0.54 |
|    | Leu | 332 | A | A | . | . | . | . | . | -0.24 | -0.20 | . | * | . | 0.45   | 1.28 |
|    | Gln | 333 | . | A | B | . | . | . | . | 0.07  | -0.20 | . | * | . | 0.30   | 0.53 |
| 25 | Val | 334 | . | A | B | . | . | . | . | 0.07  | -0.20 | . | * | . | 0.30   | 0.68 |
|    | Arg | 335 | A | A | . | . | . | . | . | -0.57 | 0.10  | . | * | . | -0.30  | 0.68 |
|    | Leu | 336 | A | A | . | . | . | . | . | -0.16 | -0.09 | . | * | . | 0.30   | 0.40 |
|    | Glu | 337 | A | A | . | . | . | . | . | 0.66  | -0.49 | * | * | . | 0.45   | 1.05 |
|    | Leu | 338 | A | A | . | . | . | . | . | -0.16 | -1.13 | . | * | . | 0.60   | 0.93 |
| 30 | Ala | 339 | A | A | . | . | . | . | . | 0.36  | -0.44 | . | * | . | 0.30   | 0.93 |
|    | Arg | 340 | A | A | . | . | . | . | . | -0.61 | -0.70 | . | * | . | 0.60   | 0.53 |
|    | Glu | 341 | A | A | . | B | . | . | . | -0.14 | -0.06 | * | . | . | 0.30   | 0.48 |
|    | Leu | 342 | A | A | . | B | . | . | . | -1.00 | -0.31 | * | . | . | 0.30   | 0.47 |
|    | Gly | 343 | A | A | . | B | . | . | . | -0.49 | -0.17 | * | * | . | 0.30   | 0.18 |
| 35 | Val | 344 | . | . | B | B | . | . | . | -0.79 | 0.21  | * | . | . | -0.30  | 0.14 |
|    | Gly | 345 | . | . | B | B | . | . | . | -1.19 | 0.90  | * | . | . | -0.60  | 0.12 |
|    | Val | 346 | . | . | B | B | . | . | . | -1.19 | 1.13  | . | * | . | -0.60  | 0.12 |
|    | Ser | 347 | . | . | B | B | . | . | . | -1.19 | 0.70  | . | . | . | -0.60  | 0.29 |
|    | Ile | 348 | . | . | B | B | . | . | . | -1.19 | 0.74  | . | . | . | -0.60  | 0.24 |
| 40 | Trp | 349 | . | . | B | B | . | . | . | -0.33 | 0.74  | . | . | . | -0.60  | 0.32 |
|    | Glu | 350 | . | . | B | B | . | . | . | -0.33 | 0.50  | * | . | . | -0.51  | 0.41 |
|    | Leu | 351 | . | . | B | . | . | . | . | -0.29 | 0.54  | . | . | . | -0.22  | 0.58 |
|    | Gly | 352 | . | . | . | . | . | T | T | 0.01  | 0.54  | * | . | F | 0.62   | 0.46 |
|    | Gln | 353 | . | . | . | . | . | T | T | 0.66  | -0.37 | * | . | F | 1.61   | 0.44 |
| 45 | Gly | 354 | . | . | . | . | . | . | T | 0.24  | 0.39  | * | . | F | 0.90   | 0.84 |
|    | Leu | 355 | . | . | . | . | . | . | T | 0.00  | 0.49  | * | . | . | 0.36   | 0.73 |
|    | Asp | 356 | . | . | B | B | . | . | . | 0.81  | 0.81  | * | . | . | -0.33  | 0.66 |
|    | Tyr | 357 | . | . | B | B | . | . | . | 0.34  | 0.41  | * | . | . | -0.27  | 1.12 |
|    | Phe | 358 | . | A | B | B | . | . | . | -0.47 | 0.67  | * | . | . | -0.36  | 1.12 |
| 50 | Tyr | 359 | . | A | B | B | . | . | . | -0.51 | 0.67  | * | . | . | -0.60  | 0.55 |
|    | Asp | 360 | . | A | B | B | . | . | . | -0.09 | 1.10  | * | . | . | -0.60  | 0.45 |
|    | Leu | 361 | . | A | B | B | . | . | . | -0.48 | 0.77  | * | . | . | -0.60  | 0.67 |
|    | Leu | 362 | A | A | . | B | . | . | . | -0.62 | 0.41  | . | . | . | -0.60  | 0.54 |

**Table 4**

(Gene No: 113 / Clone ID: HCE3Q10)

| 5  | Res Position | I | II | III | IV | V | VI | VII | VIII  | IX    | X | XI | XII | XIII  | XIV  |
|----|--------------|---|----|-----|----|---|----|-----|-------|-------|---|----|-----|-------|------|
|    | Met 1        | . | .  | B   | .  | . | .  | .   | -0.39 | 0.26  | . | .  | .   | -0.10 | 0.57 |
|    | Gly 2        | A | .  | .   | .  | . | .  | .   | -0.59 | 0.33  | . | .  | .   | -0.10 | 0.45 |
|    | Ala 3        | A | A  | .   | .  | . | .  | .   | -0.50 | 0.40  | . | .  | .   | -0.30 | 0.36 |
| 10 | Pro 4        | A | A  | .   | .  | . | .  | .   | -0.92 | 0.36  | . | .  | .   | -0.30 | 0.48 |
|    | Ala 5        | A | A  | .   | .  | . | .  | .   | -1.34 | 0.43  | . | .  | .   | -0.60 | 0.40 |
|    | Ala 6        | A | A  | .   | .  | . | .  | .   | -1.56 | 0.69  | . | .  | .   | -0.60 | 0.33 |
|    | Ser 7        | A | A  | .   | .  | . | .  | .   | -2.02 | 0.87  | . | .  | .   | -0.60 | 0.18 |
|    | Leu 8        | A | A  | .   | .  | . | .  | .   | -2.24 | 1.13  | . | .  | .   | -0.60 | 0.14 |
| 15 | Leu 9        | A | A  | .   | .  | . | .  | .   | -2.84 | 1.31  | . | .  | .   | -0.60 | 0.12 |
|    | Leu 10       | A | A  | .   | .  | . | .  | .   | -3.07 | 1.50  | . | .  | .   | -0.60 | 0.07 |
|    | Leu 11       | A | A  | .   | .  | . | .  | .   | -3.18 | 1.80  | . | .  | .   | -0.60 | 0.07 |
|    | Leu 12       | A | A  | .   | .  | . | .  | .   | -3.47 | 1.90  | . | .  | .   | -0.60 | 0.08 |
|    | Leu 13       | A | A  | .   | .  | . | .  | .   | -3.32 | 1.71  | . | .  | .   | -0.60 | 0.09 |
| 20 | Leu 14       | A | A  | .   | .  | . | .  | .   | -3.18 | 1.60  | . | .  | .   | -0.60 | 0.06 |
|    | Phe 15       | . | A  | B   | .  | . | .  | .   | -2.66 | 1.49  | . | .  | .   | -0.60 | 0.04 |
|    | Ala 16       | . | A  | B   | .  | . | .  | .   | -2.43 | 1.71  | . | .  | .   | -0.60 | 0.05 |
|    | Cys 17       | . | A  | B   | .  | . | .  | .   | -1.83 | 1.53  | . | .  | .   | -0.60 | 0.06 |
|    | Cys 18       | . | A  | B   | .  | . | .  | .   | -1.37 | 1.27  | . | .  | .   | -0.60 | 0.11 |
| 25 | Trp 19       | . | A  | B   | .  | . | .  | .   | -0.90 | 0.91  | . | .  | .   | -0.60 | 0.11 |
|    | Ala 20       | . | .  | .   | .  | . | T  | C   | -0.79 | 0.84  | . | .  | .   | 0.00  | 0.20 |
|    | Pro 21       | . | .  | .   | .  | T | T  | .   | -0.20 | 0.77  | * | .  | F   | 0.35  | 0.37 |
|    | Gly 22       | . | .  | .   | .  | T | T  | .   | -0.34 | 0.60  | . | .  | F   | 0.35  | 0.57 |
| 30 | Gly 23       | . | .  | .   | .  | T | T  | .   | 0.02  | 0.37  | * | .  | F   | 0.65  | 0.47 |
|    | Ala 24       | . | .  | .   | .  | . | .  | C   | 0.31  | 0.26  | * | .  | F   | 0.25  | 0.40 |
|    | Asn 25       | . | .  | .   | .  | . | .  | C   | 0.90  | 0.23  | * | *  | F   | 0.25  | 0.71 |
|    | Leu 26       | . | .  | B   | .  | . | .  | .   | 0.77  | -0.20 | * | *  | F   | 0.80  | 1.19 |
|    | Ser 27       | . | .  | B   | .  | . | T  | .   | 0.87  | -0.20 | . | *  | F   | 1.00  | 1.17 |
| 35 | Gln 28       | . | .  | .   | .  | T | T  | .   | 0.92  | 0.06  | . | *  | F   | 0.80  | 1.14 |
|    | Asp 29       | . | .  | .   | .  | T | T  | .   | 1.51  | 0.57  | . | *  | F   | 0.50  | 1.45 |
|    | Gly 30       | . | .  | .   | .  | . | T  | C   | 1.51  | 0.29  | . | *  | F   | 0.60  | 1.87 |
|    | Tyr 31       | . | A  | .   | .  | T | .  | .   | 2.32  | -0.10 | . | .  | .   | 0.85  | 1.87 |
|    | Trp 32       | . | A  | B   | .  | . | .  | .   | 2.62  | -0.10 | . | .  | F   | 0.60  | 1.94 |
| 40 | Gln 33       | . | A  | B   | .  | . | .  | .   | 1.81  | -0.10 | . | .  | F   | 0.60  | 3.28 |
|    | Glu 34       | . | A  | B   | .  | . | .  | .   | 1.81  | 0.16  | . | *  | F   | 0.00  | 1.72 |
|    | Gln 35       | A | A  | .   | .  | . | .  | .   | 1.34  | -0.60 | . | .  | F   | 0.90  | 2.84 |
|    | Asp 36       | A | A  | .   | .  | . | .  | .   | 1.24  | -0.83 | . | .  | F   | 0.90  | 1.35 |
|    | Leu 37       | A | A  | .   | .  | . | .  | .   | 1.22  | -0.80 | . | .  | F   | 0.75  | 0.77 |
| 45 | Glu 38       | A | A  | .   | .  | . | .  | .   | 0.41  | -0.31 | . | .  | F   | 0.45  | 0.64 |
|    | Leu 39       | A | A  | .   | .  | . | .  | .   | -0.18 | -0.03 | . | *  | .   | 0.30  | 0.32 |
|    | Gly 40       | A | A  | .   | .  | . | .  | .   | -0.39 | 0.47  | . | .  | .   | -0.60 | 0.39 |
|    | Thr 41       | A | A  | .   | .  | . | .  | .   | -1.20 | 0.21  | . | *  | .   | -0.30 | 0.35 |
|    | Leu 42       | A | A  | .   | .  | . | .  | .   | -0.39 | 0.90  | . | .  | .   | -0.60 | 0.35 |
| 50 | Ala 43       | A | A  | .   | .  | . | .  | .   | -0.39 | 0.21  | . | .  | .   | -0.30 | 0.59 |
|    | Pro 44       | A | A  | .   | .  | . | .  | .   | -0.17 | -0.21 | * | .  | .   | 0.30  | 0.70 |
|    | Leu 45       | A | A  | .   | .  | . | .  | .   | -0.71 | -0.20 | * | .  | .   | 0.30  | 0.86 |
|    | Asp 46       | A | A  | .   | .  | . | .  | .   | -0.70 | -0.20 | * | .  | .   | 0.30  | 0.60 |
|    | Glu 47       | A | A  | .   | .  | . | .  | .   | -0.19 | -0.31 | * | .  | .   | 0.30  | 0.52 |
| 55 | Ala 48       | A | .  | .   | B  | . | .  | .   | 0.09  | -0.36 | * | *  | .   | 0.30  | 0.84 |
|    | Ile 49       | . | .  | B   | B  | . | .  | .   | -0.56 | -0.56 | * | .  | F   | 0.75  | 0.73 |
|    | Ser 50       | . | .  | B   | B  | . | .  | .   | -0.03 | 0.09  | * | .  | F   | -0.15 | 0.31 |
|    | Ser 51       | . | .  | B   | B  | . | .  | .   | -0.33 | 1.00  | . | .  | F   | -0.45 | 0.33 |
|    | Thr 52       | . | .  | B   | B  | . | .  | .   | -0.63 | 0.89  | . | .  | F   | -0.45 | 0.62 |
| 60 | Val 53       | . | .  | .   | B  | T | .  | .   | -0.26 | 0.59  | * | .  | F   | -0.05 | 0.62 |
|    | Trp 54       | . | .  | .   | B  | T | .  | .   | 0.63  | 0.63  | * | .  | F   | -0.05 | 0.72 |
|    | Ser 55       | . | .  | .   | B  | . | .  | C   | 0.33  | 0.24  | * | .  | F   | 0.05  | 0.83 |
|    | Ser 56       | . | .  | .   | .  | . | T  | C   | -0.18 | 0.37  | * | .  | F   | 0.60  | 1.11 |

825

|    |     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
| 5  | Pro | 57  | . | . | . | . | . | T | C | -0.46 | 0.41  | * | . | F | 0.15  | 0.87 |
|    | Asp | 58  | . | . | . | . | T | T | . | 0.10  | 0.00  | * | . | F | 1.25  | 0.65 |
|    | Met | 59  | . | . | B | . | . | T | . | 0.39  | 0.00  | . | . | . | 0.70  | 0.65 |
|    | Leu | 60  | . | . | B | . | . | . | . | 0.69  | 0.01  | . | . | . | 0.24  | 0.73 |
|    | Ala | 61  | . | . | B | . | . | . | . | 0.69  | -0.41 | . | . | . | 1.18  | 0.73 |
|    | Ser | 62  | . | . | B | . | . | T | . | 0.90  | -0.03 | . | . | F | 1.87  | 0.99 |
|    | Gln | 63  | . | . | . | . | T | T | . | 0.69  | -0.24 | . | . | F | 2.76  | 2.08 |
|    | Asp | 64  | . | . | . | . | T | T | . | 1.00  | -0.50 | . | . | F | 3.40  | 3.19 |
| 10 | Ser | 65  | . | . | . | . | . | T | C | 1.50  | -0.09 | * | . | F | 2.56  | 2.50 |
|    | Gln | 66  | . | . | . | . | . | . | C | 1.79  | 0.01  | . | . | F | 1.66  | 2.08 |
|    | Pro | 67  | . | . | . | . | T | . | . | 2.09  | 0.00  | . | . | F | 2.36  | 1.67 |
|    | Trp | 68  | . | . | . | . | . | . | C | 2.09  | 0.00  | . | . | F | 2.06  | 2.08 |
|    | Thr | 69  | . | . | . | . | . | T | C | 1.78  | -0.39 | . | . | F | 2.16  | 2.08 |
|    | Ser | 70  | . | . | . | . | . | T | C | 1.22  | -0.30 | . | . | F | 2.40  | 1.95 |
| 15 | Asp | 71  | . | . | B | . | . | T | . | 0.37  | -0.09 | . | . | F | 1.96  | 1.37 |
|    | Glu | 72  | . | . | B | . | . | T | . | -0.01 | -0.36 | . | . | F | 1.57  | 0.71 |
|    | Thr | 73  | . | . | B | . | . | . | . | -0.07 | -0.34 | . | . | F | 1.13  | 0.53 |
|    | Val | 74  | . | . | B | . | . | . | . | -0.10 | -0.30 | . | . | . | 0.74  | 0.32 |
|    | Val | 75  | . | . | B | . | . | T | . | -0.11 | 0.13  | . | . | . | 0.10  | 0.18 |
| 20 | Ala | 76  | A | . | . | . | . | T | . | -0.97 | 0.61  | . | . | . | -0.20 | 0.18 |
|    | Gly | 77  | A | . | . | . | . | T | . | -1.82 | 0.77  | . | . | F | -0.05 | 0.18 |
|    | Gly | 78  | A | . | . | . | . | T | . | -2.32 | 0.77  | * | * | F | -0.05 | 0.18 |
|    | Thr | 79  | A | . | . | B | . | . | . | -1.42 | 0.81  | * | * | F | -0.45 | 0.15 |
|    | Val | 80  | A | . | . | B | B | . | . | -1.23 | 0.31  | . | * | . | -0.30 | 0.30 |
| 25 | Val | 81  | . | . | B | B | . | . | . | -0.64 | 0.46  | . | * | . | -0.60 | 0.16 |
|    | Leu | 82  | . | . | B | B | . | . | . | -1.16 | 0.43  | * | * | . | -0.60 | 0.19 |
|    | Lys | 83  | . | . | B | B | . | . | . | -0.77 | 0.59  | * | * | . | -0.60 | 0.19 |
|    | Cys | 84  | . | . | B | B | . | . | . | -0.46 | -0.06 | . | * | . | 0.30  | 0.52 |
|    | Gln | 85  | A | . | . | B | . | . | . | 0.37  | -0.70 | . | * | . | 0.75  | 1.05 |
| 30 | Val | 86  | A | . | . | B | B | . | . | 1.22  | -0.89 | * | * | . | 0.60  | 0.72 |
|    | Lys | 87  | . | . | B | B | . | . | . | 2.03  | -0.89 | * | * | F | 1.24  | 2.32 |
|    | Asp | 88  | A | . | . | . | . | . | . | 1.69  | -1.46 | . | * | F | 1.78  | 2.24 |
|    | His | 89  | A | . | . | . | . | . | . | 2.06  | -1.47 | . | * | F | 2.12  | 4.04 |
|    | Glu | 90  | A | . | . | . | . | . | . | 1.24  | -1.73 | * | * | F | 2.46  | 2.71 |
| 35 | Asp | 91  | . | . | . | . | T | T | . | 2.10  | -1.04 | * | * | F | 3.40  | 1.34 |
|    | Ser | 92  | . | . | . | . | T | T | . | 1.77  | -0.64 | . | * | F | 3.06  | 1.70 |
|    | Ser | 93  | . | . | . | . | T | T | . | 1.47  | -0.23 | . | . | F | 2.42  | 1.03 |
|    | Leu | 94  | . | . | . | . | T | T | . | 1.50  | 0.16  | . | * | . | 1.18  | 0.83 |
|    | Gln | 95  | . | . | . | . | T | . | . | 1.29  | 0.56  | * | * | . | 0.34  | 0.99 |
| 40 | Trp | 96  | . | . | . | . | T | . | . | 0.70  | 0.60  | * | * | . | 0.15  | 1.15 |
|    | Ser | 97  | . | . | . | . | . | . | C | 1.00  | 0.71  | * | * | F | 0.10  | 1.41 |
|    | Asn | 98  | . | . | . | . | . | T | C | 1.30  | 0.43  | * | * | F | 0.30  | 1.41 |
|    | Pro | 99  | . | . | . | . | . | T | C | 1.80  | 0.43  | * | * | F | 0.30  | 2.31 |
|    | Ala | 100 | . | . | . | . | T | T | . | 0.99  | 0.00  | * | . | F | 1.40  | 2.49 |
| 45 | Gln | 101 | . | . | B | . | . | T | . | 1.03  | 0.30  | * | . | F | 0.40  | 1.28 |
|    | Gln | 102 | . | . | B | B | . | . | . | 0.63  | 0.66  | * | . | F | -0.30 | 1.30 |
|    | Thr | 103 | . | . | B | B | . | . | . | 0.29  | 1.01  | * | . | F | -0.30 | 1.11 |
|    | Leu | 104 | . | . | B | B | . | . | . | 0.50  | 0.94  | * | . | . | -0.60 | 0.63 |
|    | Tyr | 105 | . | . | B | . | . | . | . | 1.13  | 0.54  | * | . | . | -0.40 | 0.63 |
| 50 | Phe | 106 | . | A | B | . | . | . | . | 1.24  | 0.14  | * | . | . | -0.30 | 0.88 |
|    | Gly | 107 | A | A | . | . | . | . | . | 0.66  | -0.34 | * | . | F | 0.60  | 2.09 |
|    | Glu | 108 | A | A | . | . | . | . | . | 0.16  | -0.53 | * | . | F | 0.90  | 1.35 |
|    | Lys | 109 | A | A | . | . | . | . | . | 1.08  | -0.60 | * | . | F | 0.90  | 1.28 |
|    | Arg | 110 | A | A | . | . | . | . | . | 1.32  | -1.39 | * | . | F | 0.90  | 2.54 |
| 55 | Ala | 111 | A | A | . | . | . | . | . | 2.02  | -1.81 | * | . | F | 0.90  | 2.45 |
|    | Leu | 112 | A | A | . | . | . | . | . | 2.48  | -1.41 | * | . | F | 0.90  | 1.97 |
|    | Arg | 113 | A | . | . | . | . | T | . | 1.59  | -1.41 | * | * | F | 1.30  | 1.97 |
|    | Asp | 114 | A | . | . | . | . | T | . | 1.54  | -0.73 | * | * | F | 1.30  | 1.37 |
|    | Asn | 115 | A | . | . | . | . | T | . | 0.62  | -0.83 | * | * | F | 1.30  | 2.87 |
| 60 | Arg | 116 | . | . | B | . | . | T | . | 0.36  | -0.83 | . | * | F | 1.30  | 1.21 |
|    | Ile | 117 | . | . | B | B | . | . | . | 0.86  | -0.19 | . | * | . | 0.30  | 0.54 |
|    | Gln | 118 | . | . | B | B | . | . | . | 0.44  | 0.30  | . | * | . | -0.30 | 0.48 |
|    | Leu | 119 | . | . | B | B | . | . | . | 0.13  | 0.29  | . | * | . | -0.30 | 0.33 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | Val | 120 | . | . | B | B | . | . | -0.08 | 0.77  | . | * | . | -0.36 | 0.68 |
|    | Thr | 121 | . | . | B | B | . | . | -0.22 | 0.51  | . | * | F | 0.03  | 0.61 |
|    | Ser | 122 | . | . | B | . | . | . | 0.67  | 0.61  | * | . | F | 0.47  | 1.00 |
| 5  | Thr | 123 | . | . | . | . | . | T | -0.14 | -0.07 | * | . | F | 2.16  | 2.33 |
|    | Pro | 124 | . | . | . | . | . | T | 0.37  | -0.03 | . | * | F | 2.40  | 1.33 |
|    | His | 125 | . | . | . | . | . | T | 0.33  | -0.13 | . | * | F | 2.16  | 1.33 |
|    | Glu | 126 | . | . | B | . | . | T | 0.34  | 0.17  | . | * | . | 0.82  | 0.65 |
|    | Leu | 127 | . | . | B | B | . | . | -0.24 | 0.07  | . | * | . | 0.18  | 0.56 |
| 10 | Ser | 128 | . | . | B | B | . | . | -0.23 | 0.33  | * | * | . | -0.06 | 0.29 |
|    | Ile | 129 | . | . | B | B | . | . | -0.02 | 0.21  | * | * | . | -0.30 | 0.22 |
|    | Ser | 130 | . | . | B | B | . | . | -0.84 | 0.61  | * | * | . | -0.60 | 0.44 |
|    | Ile | 131 | . | . | B | B | . | . | -1.43 | 0.57  | . | * | . | -0.60 | 0.24 |
|    | Ser | 132 | . | . | B | B | . | . | -1.43 | 0.69  | . | * | . | -0.60 | 0.35 |
| 15 | Asn | 133 | . | A | B | . | . | . | -1.72 | 0.69  | . | . | . | -0.60 | 0.21 |
|    | Val | 134 | . | A | B | . | . | . | -0.83 | 0.80  | . | . | . | -0.60 | 0.31 |
|    | Ala | 135 | . | A | B | . | . | . | -0.53 | 0.11  | . | . | . | -0.30 | 0.38 |
|    | Leu | 136 | A | A | . | . | . | . | 0.01  | -0.27 | . | . | . | 0.30  | 0.41 |
|    | Ala | 137 | A | A | . | . | . | . | 0.31  | -0.24 | . | . | . | 0.30  | 0.55 |
| 20 | Asp | 138 | A | A | . | . | . | . | 0.07  | -0.89 | . | . | F | 0.75  | 0.95 |
|    | Glu | 139 | A | A | . | . | . | . | 0.61  | -0.63 | . | . | F | 0.90  | 1.80 |
|    | Gly | 140 | A | . | . | . | . | . | 0.53  | -0.83 | * | . | F | 1.10  | 2.57 |
|    | Glu | 141 | A | . | . | . | . | . | 1.04  | -0.76 | * | * | F | 0.95  | 0.82 |
|    | Tyr | 142 | A | . | . | . | . | T | 0.74  | -0.37 | * | . | . | 0.70  | 0.64 |
| 25 | Thr | 143 | A | . | . | . | . | T | 0.04  | 0.31  | * | . | . | 0.10  | 0.45 |
|    | Cys | 144 | . | . | B | . | . | T | -0.27 | 0.67  | . | * | . | -0.20 | 0.23 |
|    | Ser | 145 | . | . | B | . | . | T | -0.52 | 1.16  | * | . | . | -0.20 | 0.21 |
|    | Ile | 146 | . | . | B | B | . | . | -0.73 | 1.01  | . | . | . | -0.60 | 0.14 |
|    | Phe | 147 | . | . | B | B | . | . | -1.34 | 0.96  | * | * | . | -0.60 | 0.41 |
| 30 | Thr | 148 | . | . | B | B | . | . | -0.92 | 1.03  | * | * | . | -0.60 | 0.23 |
|    | Met | 149 | . | . | B | B | . | . | -0.57 | 0.64  | * | * | . | -0.60 | 0.64 |
|    | Pro | 150 | . | . | B | B | . | . | -0.86 | 0.44  | * | . | . | -0.45 | 1.06 |
|    | Val | 151 | A | . | . | B | . | . | 0.08  | 0.16  | * | . | . | -0.30 | 0.74 |
|    | Arg | 152 | A | . | . | B | . | . | 0.48  | -0.33 | * | * | F | 0.60  | 1.50 |
| 35 | Thr | 153 | A | . | . | B | . | . | -0.02 | -0.56 | * | * | F | 0.90  | 1.30 |
|    | Ala | 154 | A | . | . | B | . | . | -0.28 | -0.30 | * | * | F | 0.60  | 1.45 |
|    | Lys | 155 | A | . | . | B | . | . | -0.38 | -0.30 | * | * | F | 0.45  | 0.55 |
|    | Ser | 156 | . | . | B | B | . | . | -0.38 | 0.19  | * | . | F | -0.15 | 0.55 |
|    | Leu | 157 | . | . | B | B | . | . | -1.30 | 0.34  | * | . | . | -0.30 | 0.40 |
| 40 | Val | 158 | . | . | B | B | . | . | -1.33 | 0.53  | * | . | . | -0.60 | 0.17 |
|    | Thr | 159 | . | . | B | B | . | . | -1.63 | 0.96  | * | . | . | -0.60 | 0.12 |
|    | Val | 160 | . | . | B | B | . | . | -1.89 | 1.26  | * | . | . | -0.60 | 0.10 |
|    | Leu | 161 | . | . | B | B | . | . | -1.59 | 1.00  | * | . | . | -0.60 | 0.22 |
|    | Gly | 162 | . | . | B | B | . | . | -0.73 | 0.76  | * | . | . | -0.60 | 0.26 |
| 45 | Ile | 163 | . | . | B | B | . | . | -0.09 | 0.27  | * | . | F | -0.15 | 0.70 |
|    | Pro | 164 | . | . | B | B | . | . | -0.67 | 0.06  | * | . | F | 0.20  | 1.32 |
|    | Gln | 165 | . | . | B | . | . | C | -0.70 | 0.06  | * | . | F | 0.05  | 0.93 |
|    | Lys | 166 | . | . | B | B | . | . | -0.20 | 0.31  | . | . | F | -0.15 | 0.93 |
|    | Pro | 167 | . | . | B | B | . | . | -0.20 | 0.11  | . | . | F | -0.15 | 0.87 |
| 50 | Ile | 168 | . | . | B | B | . | . | 0.44  | 0.11  | * | . | . | -0.30 | 0.50 |
|    | Ile | 169 | . | . | B | B | . | . | 0.70  | 0.47  | * | . | . | -0.60 | 0.39 |
|    | Thr | 170 | . | . | B | B | . | . | 0.40  | 0.47  | * | . | . | -0.60 | 0.50 |
|    | Gly | 171 | . | . | B | . | . | . | 0.06  | 0.43  | * | . | F | 0.05  | 0.96 |
|    | Tyr | 172 | . | . | B | . | . | T | -0.54 | 0.13  | * | * | F | 1.00  | 1.84 |
| 55 | Lys | 173 | . | . | . | . | . | T | 0.46  | 0.13  | * | * | F | 1.50  | 1.05 |
|    | Ser | 174 | . | . | . | . | . | T | 1.34  | -0.36 | * | * | F | 2.40  | 2.08 |
|    | Ser | 175 | . | . | . | . | . | T | 1.70  | -0.79 | * | * | F | 3.00  | 2.30 |
|    | Leu | 176 | . | A | B | . | . | . | 2.04  | -1.54 | * | * | F | 2.10  | 2.30 |
|    | Arg | 177 | A | A | . | . | . | . | 1.98  | -1.54 | * | * | F | 1.80  | 2.87 |
| 60 | Glu | 178 | A | A | . | . | . | . | 1.34  | -1.44 | * | * | F | 1.50  | 3.09 |
|    | Lys | 179 | A | A | . | . | . | . | 1.33  | -1.33 | . | * | F | 1.20  | 3.79 |
|    | Asp | 180 | A | A | . | . | . | . | 0.82  | -1.53 | . | * | F | 0.90  | 2.79 |
|    | Thr | 181 | A | A | . | . | . | . | 1.63  | -0.84 | . | * | F | 0.90  | 1.33 |
|    | Ala | 182 | A | A | . | . | . | . | 0.86  | -0.44 | . | * | F | 0.60  | 1.07 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | Thr | 183 | . | A | B | . | . | . | 0.86  | 0.13  | . | * | . | -0.30 | 0.34 |
|    | Leu | 184 | . | A | B | . | . | . | 0.51  | 0.53  | . | * | . | -0.60 | 0.41 |
|    | Asn | 185 | . | A | B | . | . | . | 0.21  | 0.43  | . | * | . | -0.60 | 0.55 |
| 5  | Cys | 186 | . | . | B | . | . | . | 0.18  | 0.31  | . | * | F | 0.39  | 0.51 |
|    | Gln | 187 | . | . | . | . | T | . | 0.47  | 0.26  | . | * | F | 1.13  | 0.61 |
|    | Ser | 188 | . | . | . | . | T | T | 0.82  | -0.04 | . | * | F | 2.27  | 0.51 |
|    | Ser | 189 | . | . | . | . | T | T | 1.42  | -0.44 | * | * | F | 2.76  | 1.89 |
|    | Gly | 190 | . | . | . | . | T | T | 0.83  | -0.59 | * | . | F | 3.40  | 1.69 |
|    | Ser | 191 | . | . | . | . | . | T | 0.91  | -0.49 | * | * | F | 2.56  | 1.27 |
| 10 | Lys | 192 | . | A | . | . | . | . | 1.02  | -0.37 | * | * | F | 1.67  | 0.96 |
|    | Pro | 193 | . | A | . | . | . | . | 0.51  | -0.76 | * | * | F | 1.78  | 1.90 |
|    | Ala | 194 | . | A | B | . | . | . | 0.50  | -0.50 | * | * | F | 1.24  | 1.17 |
|    | Ala | 195 | . | A | B | B | . | . | 0.56  | -0.40 | * | * | . | 0.30  | 0.84 |
|    | Arg | 196 | . | A | B | B | . | . | 0.97  | 0.51  | * | * | . | -0.60 | 0.57 |
| 15 | Leu | 197 | . | A | B | B | . | . | 0.97  | 0.09  | * | * | . | 0.19  | 1.11 |
|    | Thr | 198 | A | A | . | B | . | . | 0.83  | -0.41 | * | * | . | 1.13  | 2.20 |
|    | Trp | 199 | A | A | . | B | . | . | 1.42  | -0.49 | * | * | . | 1.47  | 1.11 |
|    | Arg | 200 | . | . | . | . | . | T | 2.01  | -0.49 | * | * | F | 2.56  | 2.25 |
|    | Lys | 201 | . | . | . | . | T | T | 1.90  | -0.77 | * | * | F | 3.40  | 2.70 |
| 20 | Gly | 202 | . | . | . | . | T | T | 1.90  | -1.26 | * | * | F | 3.06  | 4.45 |
|    | Asp | 203 | . | . | . | . | . | T | 2.18  | -1.49 | * | * | F | 2.52  | 1.87 |
|    | Gln | 204 | . | A | . | . | . | . | 2.12  | -0.99 | * | * | F | 1.78  | 1.28 |
|    | Glu | 205 | . | A | . | . | . | . | 2.01  | -0.56 | * | * | F | 1.44  | 1.28 |
|    | Leu | 206 | . | A | . | . | . | . | 1.76  | -0.99 | * | * | F | 1.10  | 1.32 |
| 25 | His | 207 | . | A | . | . | T | . | 1.79  | -0.56 | * | * | F | 1.64  | 1.18 |
|    | Gly | 208 | . | A | . | . | . | . | 1.90  | -0.47 | * | * | F | 1.33  | 0.98 |
|    | Glu | 209 | . | . | . | . | . | T | 1.01  | -0.47 | * | * | F | 2.22  | 2.34 |
|    | Pro | 210 | . | . | . | . | . | T | 1.01  | -0.47 | * | * | F | 2.56  | 1.20 |
|    | Thr | 211 | . | . | . | . | T | T | 1.82  | -0.57 | * | * | F | 3.40  | 2.11 |
| 30 | Arg | 212 | . | . | B | . | . | T | 1.86  | -1.00 | * | * | F | 2.66  | 2.11 |
|    | Ile | 213 | . | . | B | . | . | . | 1.99  | -1.00 | * | * | F | 2.46  | 2.28 |
|    | Gln | 214 | . | . | B | . | . | . | 1.99  | -1.00 | * | * | F | 2.46  | 2.44 |
|    | Glu | 215 | . | . | B | . | . | . | 1.86  | -1.09 | * | * | F | 2.46  | 2.00 |
|    | Asp | 216 | . | . | . | . | . | T | 2.21  | -0.66 | * | * | F | 2.86  | 2.83 |
| 35 | Pro | 217 | . | . | . | . | T | T | 1.79  | -1.34 | . | * | F | 3.40  | 3.26 |
|    | Asn | 218 | . | . | . | . | T | T | 1.98  | -1.26 | . | * | F | 3.06  | 2.72 |
|    | Gly | 219 | . | . | . | . | T | T | 1.67  | -0.47 | . | * | F | 2.42  | 1.41 |
|    | Lys | 220 | . | . | . | B | T | . | 0.81  | 0.01  | . | . | F | 1.08  | 1.32 |
| 40 | Thr | 221 | . | . | B | B | . | . | 0.51  | 0.23  | . | . | F | 0.19  | 0.61 |
|    | Phe | 222 | . | . | B | B | . | . | 0.42  | 0.21  | . | . | F | -0.15 | 0.82 |
|    | Thr | 223 | . | . | B | B | . | . | 0.12  | 0.17  | . | * | . | -0.30 | 0.55 |
|    | Val | 224 | . | . | B | . | . | T | -0.39 | 0.56  | . | . | F | -0.05 | 0.51 |
|    | Ser | 225 | . | . | B | . | . | T | -0.74 | 0.71  | . | * | F | -0.05 | 0.44 |
|    | Ser | 226 | . | . | . | . | . | T | -1.13 | 0.41  | . | * | F | 0.15  | 0.44 |
| 45 | Ser | 227 | . | . | . | . | . | T | -0.43 | 0.71  | . | * | F | 0.15  | 0.51 |
|    | Val | 228 | . | . | B | B | . | . | -0.98 | 0.47  | . | * | F | -0.45 | 0.66 |
|    | Thr | 229 | . | . | B | B | . | . | -0.43 | 0.73  | * | * | . | -0.60 | 0.37 |
|    | Phe | 230 | . | . | B | B | . | . | -0.02 | 0.83  | * | * | . | -0.60 | 0.39 |
|    | Gln | 231 | . | . | B | B | . | . | 0.28  | 0.44  | * | * | . | -0.45 | 1.04 |
| 50 | Val | 232 | . | . | B | B | . | . | 0.58  | -0.20 | * | * | . | 0.79  | 1.25 |
|    | Thr | 233 | . | . | B | B | . | . | 1.43  | -0.69 | * | * | F | 1.58  | 2.41 |
|    | Arg | 234 | . | . | B | B | . | . | 1.40  | -1.47 | * | . | F | 1.92  | 2.32 |
|    | Glu | 235 | . | . | . | B | T | . | 1.51  | -1.44 | * | . | F | 2.66  | 3.10 |
|    | Asp | 236 | . | . | . | . | T | T | 1.21  | -1.59 | . | . | F | 3.40  | 2.17 |
| 55 | Asp | 237 | . | . | . | . | T | T | 1.18  | -1.69 | * | . | F | 3.06  | 1.48 |
|    | Gly | 238 | . | . | . | . | T | T | 0.63  | -1.00 | . | . | F | 2.57  | 0.60 |
|    | Ala | 239 | A | . | . | . | . | T | -0.14 | -0.36 | . | . | . | 1.38  | 0.27 |
|    | Ser | 240 | . | . | B | B | . | . | -0.44 | 0.21  | * | . | . | 0.04  | 0.09 |
|    | Ile | 241 | . | . | B | B | . | . | -1.30 | 0.60  | * | . | . | -0.60 | 0.12 |
| 60 | Val | 242 | . | . | B | B | . | . | -1.30 | 0.81  | * | . | . | -0.60 | 0.09 |
|    | Cys | 243 | . | . | B | B | . | . | -0.99 | 0.71  | * | * | . | -0.60 | 0.10 |
|    | Ser | 244 | . | . | B | B | . | . | -0.40 | 0.83  | . | * | . | -0.60 | 0.20 |
|    | Val | 245 | . | . | B | B | . | . | -0.40 | 0.14  | . | . | . | -0.30 | 0.46 |

|    |     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | Asn | 246 | A | . | . | B | . | . | . | -0.32 | -0.11 | * | . | . | 0.45  | 1.16 |
|    | His | 247 | A | A | . | . | . | . | . | 0.58  | 0.00  | * | . | . | 0.30  | 0.71 |
|    | Glu | 248 | A | A | . | . | . | . | . | 0.90  | -0.39 | * | . | F | 0.60  | 1.92 |
| 5  | Ser | 249 | A | A | . | . | . | . | . | 0.61  | -0.60 | * | . | F | 0.90  | 1.18 |
|    | Leu | 250 | A | A | . | . | . | . | . | 1.47  | -0.50 | * | * | F | 0.75  | 0.88 |
|    | Lys | 251 | A | A | . | . | . | . | . | 1.58  | -1.00 | * | * | F | 0.75  | 0.85 |
|    | Gly | 252 | A | . | . | . | . | T | . | 1.31  | -1.00 | * | * | F | 1.60  | 1.24 |
|    | Ala | 253 | A | . | . | . | . | T | . | 1.00  | -1.00 | * | * | F | 1.90  | 2.01 |
| 10 | Asp | 254 | A | . | . | . | . | T | . | 1.00  | -1.20 | * | * | F | 2.20  | 1.45 |
|    | Arg | 255 | A | . | . | . | . | T | . | 1.81  | -0.81 | * | * | F | 2.50  | 1.96 |
|    | Ser | 256 | . | . | . | . | . | T | C | 1.88  | -0.84 | * | * | F | 3.00  | 3.37 |
|    | Thr | 257 | . | . | . | . | . | T | C | 1.33  | -1.34 | * | * | F | 2.70  | 3.95 |
|    | Ser | 258 | . | . | . | . | . | T | C | 1.92  | -0.66 | * | * | F | 2.40  | 1.41 |
| 15 | Gln | 259 | . | . | B | . | . | T | . | 1.07  | -0.66 | * | * | F | 1.90  | 1.83 |
|    | Arg | 260 | . | . | B | B | . | . | . | 0.14  | -0.40 | * | * | F | 0.75  | 0.94 |
|    | Ile | 261 | . | . | B | B | . | . | . | 0.20  | -0.20 | * | * | F | 0.45  | 0.58 |
|    | Glu | 262 | . | . | B | B | . | . | . | 0.20  | 0.17  | . | * | . | -0.30 | 0.52 |
|    | Val | 263 | . | . | B | B | . | . | . | 0.29  | 0.26  | . | * | . | -0.30 | 0.39 |
| 20 | Leu | 264 | . | . | B | B | . | . | . | -0.02 | 0.69  | * | * | . | -0.60 | 0.85 |
|    | Tyr | 265 | . | . | B | B | . | . | . | -0.72 | 0.49  | * | * | . | -0.60 | 0.71 |
|    | Thr | 266 | . | . | B | . | . | T | . | -0.43 | 0.99  | * | * | . | -0.20 | 0.96 |
|    | Pro | 267 | . | . | . | . | . | T | C | -1.32 | 0.96  | * | * | F | 0.30  | 1.16 |
|    | Thr | 268 | . | . | B | . | . | T | . | -0.36 | 0.96  | * | * | . | -0.20 | 0.52 |
| 25 | Ala | 269 | . | . | B | . | . | T | . | 0.24  | 0.20  | . | * | . | 0.10  | 0.70 |
|    | Met | 270 | . | . | B | . | . | . | . | 0.49  | 0.14  | . | * | . | -0.10 | 0.70 |
|    | Ile | 271 | . | . | B | . | . | . | . | 0.59  | -0.29 | . | * | . | 0.50  | 0.81 |
|    | Arg | 272 | . | . | B | . | . | T | . | 0.59  | -0.34 | . | * | . | 0.85  | 1.24 |
|    | Pro | 273 | . | . | . | . | T | T | . | 0.87  | -0.41 | . | * | F | 1.40  | 1.94 |
| 30 | Asp | 274 | . | . | . | . | . | T | C | 1.24  | -0.53 | * | * | F | 1.50  | 3.77 |
|    | Pro | 275 | . | . | . | . | . | T | C | 1.96  | -0.79 | * | * | F | 1.84  | 2.98 |
|    | Pro | 276 | . | . | . | . | . | . | C | 2.84  | -0.79 | * | * | F | 1.98  | 3.77 |
|    | His | 277 | . | . | . | . | . | T | C | 2.39  | -1.21 | * | . | F | 2.52  | 3.91 |
|    | Pro | 278 | . | . | . | . | . | T | C | 2.60  | -0.79 | * | . | F | 2.86  | 2.50 |
| 35 | Arg | 279 | . | . | . | . | T | T | . | 2.64  | -0.81 | * | * | F | 3.40  | 2.80 |
|    | Glu | 280 | A | . | . | . | . | T | . | 2.04  | -1.24 | * | * | F | 2.66  | 4.12 |
|    | Gly | 281 | A | A | . | . | . | . | . | 1.44  | -1.06 | * | * | F | 1.92  | 2.20 |
|    | Gln | 282 | A | A | . | . | . | . | . | 0.67  | -0.80 | * | * | F | 1.43  | 0.93 |
|    | Lys | 283 | A | A | . | . | . | . | . | 0.84  | -0.11 | * | * | F | 0.79  | 0.44 |
| 40 | Leu | 284 | A | . | . | . | . | . | . | 0.07  | 0.39  | * | * | F | -0.15 | 0.61 |
|    | Leu | 285 | . | A | B | . | . | . | . | 0.07  | 0.53  | * | * | . | -0.60 | 0.19 |
|    | Leu | 286 | . | A | B | . | . | . | . | 0.07  | 0.13  | * | * | . | -0.30 | 0.16 |
|    | His | 287 | . | A | B | . | . | . | . | 0.18  | 0.56  | * | * | . | -0.26 | 0.19 |
|    | Cys | 288 | . | A | B | . | . | . | . | -0.21 | -0.13 | * | * | . | 0.98  | 0.46 |
| 45 | Glu | 289 | . | A | . | . | T | . | . | 0.60  | -0.39 | . | * | F | 1.87  | 0.56 |
|    | Gly | 290 | . | . | . | . | T | T | . | 1.20  | -0.67 | . | * | F | 2.91  | 0.66 |
|    | Arg | 291 | . | . | . | . | T | T | . | 1.16  | -0.74 | . | * | F | 3.40  | 1.89 |
|    | Gly | 292 | . | . | . | . | T | T | . | 0.98  | -0.67 | . | * | F | 2.91  | 0.81 |
|    | Asn | 293 | . | . | . | . | . | T | C | 1.64  | -0.24 | . | * | F | 2.22  | 1.27 |
| 50 | Pro | 294 | . | . | . | . | . | . | C | 1.64  | -0.27 | . | * | F | 1.68  | 1.12 |
|    | Val | 295 | . | . | . | . | . | . | C | 1.74  | 0.13  | * | * | F | 0.74  | 1.96 |
|    | Pro | 296 | . | . | B | . | . | . | . | 0.82  | 0.46  | * | * | F | -0.10 | 1.91 |
|    | Gln | 297 | . | A | B | . | . | . | . | 0.88  | 0.74  | . | . | F | -0.30 | 1.02 |
|    | Gln | 298 | . | A | B | . | . | . | . | 0.88  | 1.23  | . | . | F | -0.30 | 1.44 |
| 55 | Tyr | 299 | . | A | B | . | . | . | . | 1.13  | 0.59  | . | . | . | -0.45 | 1.62 |
|    | Leu | 300 | . | A | B | . | . | . | . | 1.99  | 0.16  | . | . | . | -0.15 | 1.87 |
|    | Trp | 301 | . | A | B | . | . | . | . | 1.86  | -0.24 | . | . | . | 0.45  | 1.87 |
|    | Glu | 302 | . | A | B | . | . | . | . | 1.56  | -0.21 | . | . | F | 0.60  | 1.18 |
|    | Lys | 303 | . | A | . | . | T | . | . | 0.70  | -0.59 | . | . | F | 1.30  | 1.92 |
| 60 | Glu | 304 | . | A | . | . | T | . | . | 0.73  | -0.63 | . | . | F | 1.30  | 1.35 |
|    | Gly | 305 | . | A | . | . | T | . | . | 1.33  | -1.11 | . | . | F | 1.30  | 1.21 |
|    | Ser | 306 | . | . | . | . | . | . | C | 0.81  | -0.69 | . | . | F | 1.15  | 0.93 |
|    | Val | 307 | . | . | . | . | . | . | C | 0.86  | 0.00  | . | . | F | 0.85  | 0.44 |
|    | Pro | 308 | . | . | . | . | . | T | C | 0.21  | 0.00  | . | . | F | 1.05  | 0.90 |

|    |     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|----|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
|    | Pro | 309 | A | . | . | . | . | T | C | -0.10 | 0.19  | . | . | F | 0.45  | 0.66 |
|    | Leu | 310 | A | . | . | . | . | T | . | 0.24  | 0.29  | . | . | F | 0.40  | 1.29 |
|    | Lys | 311 | A | . | . | . | . | T | . | 0.54  | 0.04  | . | . | F | 0.40  | 1.45 |
| 5  | Met | 312 | A | A | . | . | . | . | . | 1.10  | -0.39 | * | . | F | 0.60  | 1.62 |
|    | Thr | 313 | A | A | . | . | . | . | . | 0.72  | -0.43 | . | * | F | 0.60  | 2.63 |
|    | Gln | 314 | A | A | . | . | . | . | . | 0.12  | -0.61 | . | * | F | 0.90  | 1.33 |
|    | Glu | 315 | A | A | . | . | . | . | . | 0.04  | 0.07  | * | * | F | 0.00  | 1.11 |
|    | Ser | 316 | A | A | . | B | . | . | . | -0.70 | 0.14  | * | . | F | -0.15 | 0.54 |
| 10 | Ala | 317 | A | A | . | B | . | . | . | -0.31 | 0.44  | . | . | . | -0.60 | 0.27 |
|    | Leu | 318 | A | A | . | B | . | . | . | -0.70 | 0.47  | . | . | . | -0.60 | 0.24 |
|    | Ile | 319 | . | A | B | B | . | . | . | -1.51 | 1.26  | . | . | . | -0.60 | 0.16 |
|    | Phe | 320 | . | A | B | B | . | . | . | -1.51 | 1.56  | * | . | . | -0.60 | 0.13 |
|    | Pro | 321 | . | A | B | . | . | . | . | -1.17 | 1.46  | * | . | . | -0.60 | 0.25 |
|    | Phe | 322 | . | . | B | . | . | . | . | -0.88 | 0.77  | * | . | . | -0.40 | 0.70 |
| 15 | Leu | 323 | . | . | B | . | . | . | . | -0.07 | 0.47  | * | . | . | 0.09  | 1.09 |
|    | Asn | 324 | . | . | . | . | T | . | . | 0.52  | -0.31 | * | . | F | 1.88  | 1.18 |
|    | Lys | 325 | . | . | . | . | T | . | . | 0.88  | -0.36 | . | . | F | 2.22  | 1.82 |
|    | Ser | 326 | . | . | . | . | T | . | . | 0.78  | -0.71 | * | . | F | 2.86  | 2.19 |
| 20 | Asp | 327 | . | . | . | . | T | T | . | 1.23  | -0.91 | . | . | F | 3.40  | 1.96 |
|    | Ser | 328 | . | . | . | . | T | T | . | 1.70  | -0.56 | . | . | F | 3.06  | 1.54 |
|    | Gly | 329 | . | . | . | . | T | T | . | 1.03  | -0.13 | . | . | F | 2.42  | 1.14 |
|    | Thr | 330 | . | . | . | . | T | T | . | 0.68  | 0.06  | . | . | F | 1.33  | 0.36 |
|    | Tyr | 331 | . | . | B | B | . | . | . | 0.39  | 0.54  | . | . | F | -0.11 | 0.39 |
| 25 | Gly | 332 | . | . | B | B | . | . | . | 0.08  | 0.66  | . | . | . | -0.60 | 0.40 |
|    | Cys | 333 | . | . | B | B | . | . | . | 0.08  | 0.71  | . | . | . | -0.60 | 0.40 |
|    | Thr | 334 | . | . | B | B | . | . | . | 0.42  | 0.61  | . | . | . | -0.60 | 0.34 |
|    | Ala | 335 | . | . | B | B | . | . | . | 0.13  | 0.26  | . | . | F | -0.15 | 0.56 |
|    | Thr | 336 | . | . | B | B | . | . | . | 0.03  | 0.44  | . | . | F | -0.30 | 1.03 |
| 30 | Ser | 337 | . | . | B | B | . | . | . | 0.08  | 0.30  | . | . | F | -0.06 | 0.71 |
|    | Asn | 338 | . | . | B | . | T | T | . | 0.50  | 0.20  | . | . | F | 0.83  | 0.94 |
|    | Met | 339 | . | . | . | . | T | T | . | 0.86  | 0.46  | . | . | F | 0.77  | 1.02 |
|    | Gly | 340 | . | . | . | . | T | T | . | 0.86  | -0.03 | . | . | F | 1.76  | 1.52 |
|    | Ser | 341 | . | . | . | . | . | T | C | 0.92  | 0.09  | . | . | F | 0.90  | 0.95 |
| 35 | Tyr | 342 | . | . | B | B | . | . | . | 0.98  | 0.44  | . | . | . | -0.09 | 1.51 |
|    | Lys | 343 | . | . | B | B | . | . | . | 0.67  | 0.59  | . | * | . | -0.18 | 2.39 |
|    | Ala | 344 | . | . | B | B | . | . | . | 0.46  | 0.64  | . | * | . | -0.27 | 2.57 |
|    | Tyr | 345 | . | . | B | B | . | . | . | 0.80  | 0.94  | . | * | . | -0.36 | 1.35 |
|    | Tyr | 346 | . | . | B | B | . | . | . | 0.24  | 0.59  | . | * | . | -0.45 | 1.09 |
| 40 | Thr | 347 | . | . | B | B | . | . | . | 0.49  | 1.23  | . | * | . | -0.60 | 0.80 |
|    | Leu | 348 | . | . | B | B | . | . | . | 0.44  | 1.13  | . | * | . | -0.36 | 0.82 |
|    | Asn | 349 | . | . | B | B | . | . | . | 0.82  | 0.37  | . | * | . | 0.18  | 0.87 |
|    | Val | 350 | . | . | B | B | . | . | . | 0.77  | 0.04  | . | * | . | 0.42  | 0.94 |
|    | Asn | 351 | . | . | . | B | T | . | . | 0.80  | -0.06 | . | * | F | 1.96  | 1.52 |
| 45 | Asp | 352 | . | . | . | . | . | T | C | 0.26  | -0.31 | . | * | F | 2.40  | 1.46 |
|    | Pro | 353 | . | . | B | . | . | T | . | 0.86  | -0.07 | . | * | F | 1.96  | 1.46 |
|    | Ser | 354 | . | . | . | . | . | T | C | 0.56  | -0.29 | . | . | F | 1.92  | 1.41 |
|    | Pro | 355 | . | . | B | . | . | T | . | 1.11  | -0.30 | . | . | F | 1.48  | 1.13 |
|    | Val | 356 | . | . | B | . | . | T | . | 0.81  | 0.09  | . | . | F | 0.49  | 0.98 |
| 50 | Pro | 357 | . | . | B | . | . | T | . | 0.51  | 0.04  | . | . | F | 0.25  | 0.98 |
|    | Ser | 358 | . | . | . | . | T | T | . | 0.41  | 0.04  | . | . | F | 0.65  | 0.85 |
|    | Ser | 359 | . | . | B | . | . | T | . | 0.47  | 0.10  | . | . | F | 0.40  | 1.65 |
|    | Ser | 360 | . | . | B | . | . | T | . | 0.64  | 0.21  | . | . | F | 0.40  | 1.67 |
|    | Ser | 361 | . | . | B | . | . | T | . | 0.91  | 0.29  | . | . | F | 0.40  | 1.70 |
| 55 | Thr | 362 | . | . | B | . | . | T | . | 0.23  | 0.40  | . | . | F | 0.40  | 1.28 |
|    | Tyr | 363 | . | . | B | . | . | T | . | -0.36 | 0.70  | . | . | . | -0.20 | 0.67 |
|    | His | 364 | . | . | B | B | . | . | . | -0.40 | 1.00  | . | . | . | -0.60 | 0.35 |
|    | Ala | 365 | . | . | B | B | . | . | . | -0.44 | 1.04  | * | . | . | -0.60 | 0.24 |
|    | Ile | 366 | . | . | B | B | . | . | . | -1.03 | 0.99  | * | . | . | -0.60 | 0.15 |
| 60 | Ile | 367 | . | . | B | B | . | . | . | -1.58 | 0.91  | . | . | . | -0.60 | 0.08 |
|    | Gly | 368 | . | . | B | B | . | . | . | -1.92 | 1.06  | * | . | . | -0.60 | 0.06 |
|    | Gly | 369 | . | . | B | B | . | . | . | -2.59 | 1.06  | * | . | . | -0.60 | 0.08 |
|    | Ile | 370 | . | . | B | B | . | . | . | -2.89 | 1.16  | . | . | . | -0.60 | 0.10 |
|    | Val | 371 | . | . | B | B | . | . | . | -2.86 | 1.16  | . | . | . | -0.60 | 0.07 |

|    |     |     |   |   |   |   |   |   |       |       |   |   |        |      |
|----|-----|-----|---|---|---|---|---|---|-------|-------|---|---|--------|------|
|    | Ala | 372 | . | . | B | B | . | . | -2.67 | 1.37  | . | . | -0.60  | 0.05 |
|    | Phe | 373 | . | . | B | B | . | . | -3.13 | 1.73  | . | . | -0.60  | 0.07 |
|    | Ile | 374 | . | . | B | B | . | . | -3.60 | 1.73  | . | . | -0.60  | 0.07 |
|    | Val | 375 | . | . | B | B | . | . | -3.52 | 1.77  | . | . | -0.60  | 0.06 |
| 5  | Phe | 376 | A | . | . | B | . | . | -3.56 | 1.96  | . | . | -0.60  | 0.06 |
|    | Leu | 377 | A | . | . | B | . | . | -3.57 | 1.86  | . | . | -0.60  | 0.06 |
|    | Leu | 378 | A | . | . | B | . | . | -3.68 | 1.79  | . | . | -0.60  | 0.08 |
|    | Leu | 379 | A | . | . | B | . | . | -3.68 | 1.83  | . | . | -0.60  | 0.07 |
|    | Ile | 380 | A | . | . | B | . | . | -3.52 | 1.73  | . | . | -0.60  | 0.06 |
| 10 | Met | 381 | A | . | . | B | . | . | -3.63 | 1.83  | . | . | -0.60  | 0.07 |
|    | Leu | 382 | A | . | . | B | . | . | -3.17 | 1.83  | . | . | -0.60  | 0.07 |
|    | Ile | 383 | A | . | . | B | . | . | -2.39 | 1.57  | . | . | -0.60  | 0.09 |
|    | Phe | 384 | A | . | . | B | . | . | -1.82 | 1.39  | . | . | -0.60  | 0.13 |
|    | Leu | 385 | A | . | . | B | . | . | -1.74 | 1.53  | . | . | -0.60  | 0.24 |
| 15 | Gly | 386 | A | . | . | B | . | . | -2.03 | 1.53  | * | * | -0.60  | 0.28 |
|    | His | 387 | A | . | . | B | . | . | -1.11 | 1.53  | * | * | -0.60  | 0.23 |
|    | Tyr | 388 | A | . | . | B | . | . | -0.26 | 0.74  | . | * | -0.60  | 0.55 |
|    | Leu | 389 | . | . | B | B | . | . | 0.49  | 0.56  | . | * | -0.32  | 0.75 |
| 20 | Ile | 390 | . | . | B | B | . | . | 0.96  | 0.13  | * | * | 0.41   | 1.11 |
|    | Arg | 391 | . | . | B | B | . | . | 0.99  | 0.06  | * | * | 0.54   | 0.70 |
|    | His | 392 | . | . | . | . | T | T | 0.78  | -0.21 | * | * | 2.37   | 1.22 |
|    | Lys | 393 | . | . | . | . | T | T | 0.21  | -0.14 | * | * | F 2.80 | 2.73 |
|    | Gly | 394 | . | . | . | . | . | T | 0.71  | -0.14 | * | * | F 2.32 | 1.15 |
|    | Thr | 395 | . | . | . | . | . | T | 1.57  | 0.34  | * | * | F 1.44 | 1.22 |
| 25 | Tyr | 396 | . | . | B | . | . | . | 1.46  | 0.34  | * | * | 0.46   | 0.83 |
|    | Leu | 397 | . | A | B | . | . | . | 0.90  | 0.34  | * | * | 0.13   | 1.45 |
|    | Thr | 398 | . | A | B | . | . | . | 0.90  | 0.41  | . | * | -0.45  | 1.02 |
|    | His | 399 | A | A | . | . | . | . | 0.90  | -0.07 | * | * | 0.79   | 1.30 |
|    | Glu | 400 | A | A | . | . | . | . | 0.91  | -0.40 | * | * | 1.13   | 1.56 |
| 30 | Ala | 401 | A | A | . | . | . | . | 1.16  | -0.70 | * | * | F 1.92 | 1.45 |
|    | Lys | 402 | . | A | . | . | T | . | 1.97  | -1.19 | * | * | F 2.66 | 1.78 |
|    | Gly | 403 | . | . | . | . | T | T | 1.69  | -1.69 | * | * | F 3.40 | 1.71 |
|    | Ser | 404 | . | . | . | . | . | T | 1.51  | -1.19 | * | * | F 2.86 | 1.71 |
| 35 | Asp | 405 | . | . | . | . | T | T | 1.51  | -1.26 | * | * | F 2.72 | 1.32 |
|    | Asp | 406 | A | . | . | . | . | T | 1.51  | -1.26 | * | * | F 2.18 | 2.23 |
|    | Ala | 407 | A | . | . | . | . | . | 1.47  | -1.19 | * | . | F 1.44 | 1.68 |
|    | Pro | 408 | A | . | . | . | . | . | 1.50  | -1.57 | . | . | F 1.10 | 1.68 |
|    | Asp | 409 | A | . | . | . | . | T | 1.21  | -1.09 | * | . | F 1.30 | 1.46 |
|    | Ala | 410 | A | . | . | . | . | T | 0.32  | -0.59 | * | . | F 1.30 | 1.46 |
| 40 | Asp | 411 | A | . | . | . | . | T | -0.57 | -0.40 | * | . | F 0.85 | 0.66 |
|    | Thr | 412 | A | . | . | . | . | T | 0.02  | -0.14 | * | . | F 0.85 | 0.28 |
|    | Ala | 413 | A | . | . | B | . | . | -0.36 | 0.26  | . | * | -0.30  | 0.44 |
|    | Ile | 414 | . | . | B | B | . | . | -0.36 | 0.26  | . | * | -0.30  | 0.27 |
|    | Ile | 415 | . | . | B | B | . | . | -0.11 | 0.26  | . | . | -0.30  | 0.32 |
| 45 | Asn | 416 | . | . | B | . | . | T | -0.46 | 0.20  | . | . | 0.10   | 0.31 |
|    | Ala | 417 | . | . | B | . | . | T | -0.14 | 0.13  | . | . | F 0.25 | 0.44 |
|    | Glu | 418 | . | . | . | . | T | T | 0.14  | -0.16 | . | . | F 1.40 | 1.09 |
|    | Gly | 419 | . | . | . | . | T | T | 0.69  | -0.46 | . | . | F 1.55 | 0.91 |
|    | Gly | 420 | . | . | . | . | T | . | 1.23  | -0.43 | . | * | F 1.65 | 0.89 |
| 50 | Gln | 421 | . | . | . | . | . | T | 1.23  | -0.50 | * | . | F 2.25 | 0.51 |
|    | Ser | 422 | . | . | . | . | . | T | 1.82  | -0.50 | . | . | F 2.55 | 0.86 |
|    | Gly | 423 | . | . | . | . | . | T | 1.87  | -0.93 | * | . | F 3.00 | 1.45 |
|    | Gly | 424 | . | . | . | . | . | T | 2.26  | -1.36 | * | . | F 2.70 | 1.68 |
|    | Asp | 425 | . | . | . | . | . | T | 2.60  | -1.76 | * | . | F 2.58 | 2.50 |
| 55 | Asp | 426 | . | . | . | . | . | T | 2.36  | -2.14 | * | . | F 2.46 | 4.38 |
|    | Lys | 427 | A | . | . | . | . | T | 1.96  | -1.81 | . | . | F 2.14 | 6.94 |
|    | Lys | 428 | A | . | . | . | . | T | 1.41  | -1.46 | . | . | F 2.02 | 3.60 |
|    | Glu | 429 | . | . | B | B | . | . | 1.37  | -0.77 | . | . | F 1.80 | 1.51 |
| 60 | Tyr | 430 | . | . | B | B | . | . | 0.98  | -0.34 | . | . | 1.02   | 0.97 |
|    | Phe | 431 | . | . | B | B | . | . | 0.59  | 0.09  | . | . | 0.24   | 0.62 |
|    | Ile | 432 | A | . | . | B | . | . | 0.16  | 0.51  | . | . | -0.24  | 0.46 |



Table 5

(Gene No:62 / Clone ID HEMAE80)

| Res | Position | I | II | III | IV | V | VI | VII | VIII  | IX    | X | XI | XII | XIII  | XIV  |
|-----|----------|---|----|-----|----|---|----|-----|-------|-------|---|----|-----|-------|------|
| Met | 1        | . | .  | B   | .  | . | .  | .   | 0.59  | -0.19 | . | *  | .   | 0.86  | 1.62 |
| Arg | 2        | . | .  | B   | .  | . | .  | .   | 0.77  | -0.19 | . | *  | .   | 1.07  | 1.25 |
| Thr | 3        | . | .  | .   | .  | . | T  | C   | 0.34  | -0.19 | . | *  | .   | 1.68  | 1.52 |
| Pro | 4        | . | .  | .   | .  | . | T  | C   | 0.52  | 0.07  | . | *  | .   | 1.29  | 1.26 |
| Gly | 5        | . | .  | .   | .  | . | T  | C   | 0.06  | -0.11 | . | *  | F   | 2.10  | 1.00 |
| Pro | 6        | . | .  | .   | .  | . | T  | C   | -0.16 | 0.53  | . | *  | F   | 0.99  | 0.51 |
| Leu | 7        | . | A  | B   | .  | . | .  | .   | -1.08 | 0.73  | . | *  | F   | 0.18  | 0.27 |
| Pro | 8        | . | A  | B   | .  | . | .  | .   | -1.58 | 0.99  | . | .  | .   | -0.18 | 0.23 |
| Val | 9        | . | A  | B   | .  | . | .  | .   | -2.18 | 1.24  | . | .  | .   | -0.39 | 0.12 |
| Leu | 10       | . | A  | B   | .  | . | .  | .   | -2.64 | 1.50  | . | .  | .   | -0.60 | 0.12 |
| Leu | 11       | . | A  | B   | .  | . | .  | .   | -3.02 | 1.50  | . | .  | .   | -0.60 | 0.06 |
| Leu | 12       | . | A  | B   | .  | . | .  | .   | -2.56 | 1.57  | . | .  | .   | -0.60 | 0.09 |
| Leu | 13       | . | A  | B   | .  | . | .  | .   | -2.93 | 1.36  | . | .  | .   | -0.60 | 0.11 |
| Leu | 14       | . | A  | B   | .  | . | .  | .   | -2.29 | 1.17  | . | .  | .   | -0.60 | 0.13 |
| Ala | 15       | . | A  | B   | .  | . | .  | .   | -2.07 | 0.91  | . | .  | .   | -0.60 | 0.24 |
| Gly | 16       | . | A  | B   | .  | . | .  | .   | -1.84 | 0.73  | . | .  | .   | -0.60 | 0.30 |
| Ala | 17       | . | .  | B   | .  | . | .  | .   | -0.92 | 0.54  | . | .  | .   | -0.40 | 0.37 |
| Pro | 18       | . | .  | B   | .  | . | .  | .   | -0.32 | -0.14 | . | .  | .   | 0.74  | 0.71 |
| Ala | 19       | . | .  | .   | .  | T | .  | .   | 0.18  | -0.21 | . | .  | .   | 1.53  | 1.11 |
| Ala | 20       | . | .  | B   | .  | . | .  | .   | 0.56  | -0.16 | . | .  | .   | 1.37  | 1.58 |
| Arg | 21       | . | .  | B   | .  | . | .  | .   | 0.69  | -0.23 | . | .  | F   | 1.76  | 1.58 |
| Pro | 22       | . | .  | .   | .  | T | .  | .   | 0.97  | -0.23 | . | .  | F   | 2.40  | 2.42 |
| Thr | 23       | . | .  | .   | .  | . | .  | C   | 0.51  | -0.24 | . | .  | F   | 1.96  | 3.46 |
| Pro | 24       | . | .  | .   | .  | . | T  | C   | 0.86  | -0.17 | . | .  | F   | 1.77  | 0.95 |
| Pro | 25       | . | .  | .   | .  | T | T  | .   | 1.14  | 0.59  | . | *  | F   | 0.83  | 0.96 |
| Thr | 26       | . | .  | .   | .  | T | T  | .   | 1.14  | 0.54  | . | *  | F   | 0.59  | 0.89 |
| Cys | 27       | . | .  | B   | .  | . | T  | .   | 0.76  | 0.06  | . | *  | .   | 0.25  | 1.13 |
| Tyr | 28       | . | .  | B   | .  | . | .  | .   | 1.18  | 0.24  | . | *  | .   | -0.10 | 0.72 |
| Ser | 29       | . | A  | B   | .  | . | .  | .   | 0.80  | -0.19 | . | *  | .   | 0.30  | 0.98 |
| Arg | 30       | . | A  | B   | .  | . | .  | .   | 0.20  | -0.17 | . | *  | .   | 0.45  | 1.85 |
| Met | 31       | . | A  | B   | .  | . | .  | .   | 0.21  | -0.06 | . | *  | .   | 0.30  | 0.97 |
| Arg | 32       | . | A  | B   | .  | . | .  | .   | 0.88  | -0.43 | . | *  | .   | 0.30  | 0.97 |
| Ala | 33       | . | A  | B   | .  | . | .  | .   | 1.12  | -0.41 | * | *  | .   | 0.30  | 0.86 |
| Leu | 34       | . | A  | .   | .  | . | .  | C   | 0.53  | -0.41 | * | *  | .   | 0.65  | 1.50 |
| Ser | 35       | . | A  | B   | .  | . | .  | .   | 0.11  | -0.34 | * | *  | F   | 0.45  | 0.54 |
| Gln | 36       | . | A  | B   | .  | . | .  | .   | 0.82  | 0.14  | * | .  | F   | -0.15 | 0.77 |
| Glu | 37       | . | A  | B   | .  | . | .  | .   | 0.71  | -0.36 | * | .  | F   | 0.60  | 1.83 |
| Ile | 38       | . | A  | B   | .  | . | .  | .   | 0.60  | -1.04 | * | .  | F   | 0.90  | 2.28 |
| Thr | 39       | . | A  | B   | .  | . | .  | .   | 1.41  | -0.64 | * | *  | F   | 0.90  | 1.14 |
| Arg | 40       | . | A  | B   | .  | . | .  | .   | 0.90  | -0.64 | * | .  | F   | 0.90  | 1.06 |
| Asp | 41       | . | A  | .   | .  | T | .  | .   | 0.09  | 0.04  | * | .  | F   | 0.40  | 1.24 |
| Phe | 42       | . | .  | B   | B  | . | .  | .   | 0.09  | 0.04  | * | .  | .   | -0.30 | 0.71 |
| Asn | 43       | . | .  | B   | B  | . | .  | .   | 0.12  | -0.04 | * | .  | .   | 0.30  | 0.63 |
| Leu | 44       | . | .  | .   | B  | . | .  | C   | 0.13  | 0.60  | . | .  | .   | -0.40 | 0.28 |
| Leu | 45       | . | .  | B   | B  | . | .  | .   | 0.02  | 0.99  | . | .  | .   | -0.60 | 0.43 |
| Gln | 46       | . | .  | B   | B  | . | .  | .   | -0.19 | 0.20  | . | .  | .   | 0.04  | 0.47 |
| Val | 47       | . | .  | .   | B  | . | .  | C   | 0.21  | 0.23  | . | .  | .   | 0.58  | 0.87 |
| Ser | 48       | . | .  | .   | B  | . | .  | C   | 0.21  | -0.07 | . | .  | F   | 1.82  | 1.42 |
| Glu | 49       | . | .  | .   | .  | . | T  | C   | 0.81  | -0.76 | . | .  | F   | 2.86  | 1.42 |
| Pro | 50       | . | .  | .   | .  | T | T  | .   | 0.96  | -0.73 | . | .  | F   | 3.40  | 2.95 |
| Ser | 51       | . | .  | .   | .  | T | T  | .   | 0.10  | -0.80 | * | *  | F   | 3.06  | 1.18 |
| Glu | 52       | . | .  | .   | .  | . | T  | C   | 1.07  | -0.54 | * | *  | F   | 2.37  | 0.51 |
| Pro | 53       | . | .  | .   | B  | T | .  | .   | 1.12  | -0.54 | * | .  | F   | 1.83  | 0.64 |
| Cys | 54       | . | .  | B   | B  | . | .  | .   | 0.31  | -0.21 | * | .  | .   | 0.64  | 0.75 |
| Val | 55       | . | .  | B   | B  | . | .  | .   | 0.31  | 0.09  | * | *  | .   | -0.30 | 0.36 |
| Arg | 56       | . | .  | B   | B  | . | .  | .   | 0.72  | 0.51  | * | *  | .   | -0.60 | 0.36 |
| Tyr | 57       | . | .  | B   | B  | . | .  | .   | -0.09 | 0.09  | * | *  | .   | -0.15 | 1.30 |
| Leu | 58       | . | .  | B   | B  | . | .  | .   | -0.12 | 0.20  | * | *  | .   | -0.15 | 1.45 |

|     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
| Pro | 59  | . | . | B | B | . | . | . | -0.27 | 0.31  | * | * | . | -0.15 | 1.16 |
| Arg | 60  | . | . | B | B | . | . | . | 0.59  | 1.00  | * | * | . | -0.60 | 0.61 |
| Leu | 61  | . | . | B | B | . | . | . | -0.41 | 0.24  | * | * | . | -0.15 | 1.24 |
| Tyr | 62  | . | . | B | B | . | . | . | -0.20 | 0.24  | * | * | . | -0.30 | 0.56 |
| Leu | 63  | . | . | B | B | . | . | . | 0.61  | 0.31  | * | * | . | -0.30 | 0.39 |
| Asp | 64  | . | . | B | B | . | . | . | 0.58  | 0.71  | * | * | . | -0.60 | 0.76 |
| Ile | 65  | . | . | B | B | . | . | . | -0.20 | 0.79  | * | * | . | -0.60 | 0.76 |
| His | 66  | . | . | B | . | . | T | . | -0.24 | 0.60  | . | * | . | -0.20 | 0.49 |
| Asn | 67  | . | . | B | . | . | T | . | -0.81 | 0.56  | . | * | . | -0.20 | 0.22 |
| Tyr | 68  | . | . | B | . | . | T | . | 0.00  | 1.24  | . | * | . | -0.20 | 0.26 |
| Cys | 69  | . | . | B | . | . | T | . | 0.04  | 0.56  | . | . | . | -0.20 | 0.32 |
| Val | 70  | . | A | B | B | . | . | . | 0.12  | 0.06  | . | * | . | -0.30 | 0.39 |
| Leu | 71  | . | A | B | B | . | . | . | 0.27  | 0.34  | * | * | . | -0.30 | 0.21 |
| Asp | 72  | . | A | B | B | . | . | . | 0.27  | -0.41 | * | . | F | 0.45  | 0.76 |
| Lys | 73  | . | A | B | . | . | . | . | -0.19 | -0.99 | * | * | F | 0.90  | 1.70 |
| Leu | 74  | . | A | B | B | . | . | . | -0.38 | -0.84 | * | . | F | 0.90  | 1.79 |
| Arg | 75  | . | A | B | B | . | . | . | -0.11 | -0.89 | * | . | F | 0.75  | 0.79 |
| Asp | 76  | . | A | B | B | . | . | . | 0.40  | -0.39 | * | . | . | 0.30  | 0.40 |
| Phe | 77  | . | A | B | B | . | . | . | 0.19  | 0.00  | * | . | . | 0.30  | 0.65 |
| Val | 78  | . | A | B | B | . | . | . | -0.07 | -0.26 | * | * | . | 0.30  | 0.52 |
| Ala | 79  | . | A | B | B | . | . | . | 0.08  | 0.17  | * | . | . | -0.30 | 0.48 |
| Ser | 80  | . | A | . | B | . | . | C | -0.32 | 0.74  | . | . | . | -0.40 | 0.30 |
| Pro | 81  | . | . | . | . | . | T | C | -0.28 | 0.87  | . | * | F | 0.15  | 0.42 |
| Pro | 82  | . | . | . | . | T | T | . | -0.43 | 0.23  | . | . | F | 0.65  | 0.83 |
| Cys | 83  | . | . | . | . | T | T | . | -0.17 | 0.37  | . | . | . | 0.50  | 0.46 |
| Trp | 84  | . | . | . | . | T | T | . | 0.42  | 0.49  | . | . | . | 0.20  | 0.30 |
| Lys | 85  | . | A | B | . | . | . | . | -0.13 | 0.46  | . | . | . | -0.60 | 0.34 |
| Val | 86  | . | A | B | . | . | . | . | 0.08  | 0.67  | . | . | . | -0.60 | 0.46 |
| Ala | 87  | . | A | B | . | . | . | . | -0.01 | 0.10  | . | . | . | -0.30 | 0.74 |
| Gln | 88  | . | A | B | . | . | . | . | -0.16 | -0.43 | . | . | . | 0.30  | 0.49 |
| Val | 89  | . | A | B | . | . | . | . | 0.18  | 0.26  | . | . | . | -0.30 | 0.55 |
| Asp | 90  | . | A | B | . | . | . | . | 0.13  | -0.39 | . | . | F | 0.60  | 1.09 |
| Ser | 91  | . | A | B | . | . | . | . | 1.03  | -0.89 | . | . | F | 0.90  | 1.05 |
| Leu | 92  | A | A | . | . | . | . | . | 1.03  | -1.29 | * | * | F | 0.90  | 2.83 |
| Lys | 93  | A | A | . | . | . | . | . | 1.14  | -1.43 | * | * | F | 0.90  | 1.71 |
| Asp | 94  | . | A | . | . | T | . | . | 2.04  | -1.43 | * | * | F | 1.30  | 2.50 |
| Lys | 95  | A | A | . | . | . | . | . | 1.23  | -1.81 | * | * | F | 0.90  | 6.06 |
| Ala | 96  | A | A | . | . | . | . | . | 1.29  | -1.81 | * | * | F | 0.90  | 2.50 |
| Arg | 97  | . | A | B | . | . | . | . | 1.79  | -1.06 | * | * | F | 0.90  | 2.34 |
| Lys | 98  | . | A | B | . | . | . | . | 0.86  | -0.57 | * | * | F | 0.90  | 1.69 |
| Leu | 99  | . | A | B | . | . | . | . | 0.26  | 0.11  | * | . | . | -0.15 | 1.17 |
| Tyr | 100 | . | A | B | . | . | . | . | 0.21  | 0.23  | * | . | . | -0.30 | 0.59 |
| Thr | 101 | . | . | B | B | . | . | . | 0.50  | 0.63  | * | . | . | -0.60 | 0.48 |
| Ile | 102 | . | . | B | B | . | . | . | -0.31 | 1.01  | * | . | . | -0.60 | 0.77 |
| Met | 103 | . | . | B | B | . | . | . | -1.02 | 1.11  | * | . | . | -0.60 | 0.43 |
| Asn | 104 | . | . | B | . | . | T | . | -0.10 | 0.93  | * | . | . | 0.04  | 0.16 |
| Ser | 105 | . | . | B | . | . | T | . | 0.26  | 0.44  | * | . | . | 0.28  | 0.44 |
| Phe | 106 | . | . | B | . | . | T | . | 0.57  | -0.24 | * | . | . | 1.42  | 0.88 |
| Cys | 107 | . | . | B | . | . | T | . | 0.64  | -0.86 | . | . | . | 1.96  | 0.91 |
| Arg | 108 | . | . | . | . | T | . | . | 0.39  | -0.57 | . | . | . | 2.40  | 0.56 |
| Arg | 109 | . | . | B | B | . | . | . | -0.31 | -0.31 | * | . | F | 1.41  | 0.48 |
| Asp | 110 | . | . | B | B | . | . | . | -0.82 | -0.31 | . | . | F | 1.17  | 0.78 |
| Leu | 111 | . | . | B | B | . | . | . | -0.93 | -0.20 | * | . | . | 0.78  | 0.33 |
| Val | 112 | . | . | B | B | . | . | . | -0.27 | 0.49  | * | . | . | -0.36 | 0.14 |
| Phe | 113 | . | . | B | B | . | . | . | -0.38 | 0.49  | * | . | . | -0.60 | 0.14 |
| Leu | 114 | . | . | B | B | . | . | . | -1.16 | 0.49  | * | . | . | -0.60 | 0.28 |
| Leu | 115 | . | . | B | B | . | . | . | -1.16 | 0.37  | . | . | . | -0.02 | 0.20 |
| Asp | 116 | . | . | . | . | T | T | . | -0.93 | 0.13  | . | . | F | 1.21  | 0.37 |
| Asp | 117 | . | . | . | . | T | T | . | -0.89 | -0.16 | . | . | F | 2.09  | 0.46 |
| Cys | 118 | . | . | . | . | T | T | . | -0.19 | -0.16 | . | . | . | 2.22  | 0.46 |
| Asn | 119 | . | . | . | . | T | T | . | 0.38  | -0.84 | . | . | . | 2.80  | 0.48 |
| Ala | 120 | . | A | B | . | . | . | . | 0.98  | -0.09 | . | . | . | 1.42  | 0.45 |
| Leu | 121 | . | A | B | . | . | . | . | 0.09  | 0.34  | . | . | . | 0.69  | 1.29 |

833

|     |     |   |   |   |   |   |   |   |       |       |   |   |   |       |      |
|-----|-----|---|---|---|---|---|---|---|-------|-------|---|---|---|-------|------|
| Glu | 122 | . | A | B | . | . | . | . | -0.12 | 0.46  | . | * | . | -0.04 | 0.56 |
| Tyr | 123 | . | A | B | . | . | . | . | -0.31 | 0.49  | . | * | . | -0.32 | 0.86 |
| Pro | 124 | . | . | B | B | . | . | . | -0.62 | 0.63  | . | * | . | -0.60 | 0.77 |
| Ile | 125 | . | . | B | B | . | . | . | -0.34 | 0.43  | . | * | . | -0.60 | 0.64 |
| Pro | 126 | . | . | B | B | . | . | . | -0.39 | 0.91  | . | * | . | -0.60 | 0.59 |
| Val | 127 | . | . | B | B | . | . | . | -1.20 | 0.80  | . | . | . | -0.60 | 0.29 |
| Thr | 128 | . | . | B | B | . | . | . | -1.17 | 1.06  | . | . | . | -0.60 | 0.34 |
| Thr | 129 | . | . | B | B | . | . | . | -0.96 | 0.80  | . | . | F | -0.11 | 0.34 |
| Val | 130 | . | . | B | B | . | . | . | 0.04  | 0.37  | . | . | F | 0.53  | 0.75 |
| Leu | 131 | . | . | B | . | . | T | . | 0.26  | -0.27 | . | * | F | 2.02  | 1.02 |
| Pro | 132 | . | . | B | . | . | T | . | 1.22  | -0.36 | . | * | F | 2.36  | 1.23 |
| Asp | 133 | . | . | . | . | T | T | . | 1.14  | -0.84 | . | * | F | 3.40  | 3.24 |
| Arg | 134 | . | . | B | . | . | T | . | 1.07  | -1.06 | . | * | . | 2.51  | 5.03 |
| Gln | 135 | . | . | B | . | . | . | . | 1.53  | -1.31 | . | * | . | 1.97  | 4.16 |
| Arg | 136 | . | . | B | . | . | . | . | 1.96  | -1.31 | . | * | . | 1.63  | 3.18 |

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 440.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
27 March 1997

Accession Number  
97979

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

|   |                               |  |  |                                   |  |
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| <input type="checkbox"/> This sheet was received with the international application |                               | <input type="checkbox"/> This sheet was received by the International Bureau on: |  |                                   |  |
| Authorized officer  |                               | Authorized officer   |  |                                   |  |

**ATCC Deposit No. 97979****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97979

## UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 442.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

04 April 1997

Accession Number

97974

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 97974****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.



**ATCC Deposit No.: 97974**

### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 442.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209080

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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**ATCC Deposit No. 209080**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: 209080**

### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 444.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
03 December 1997

Accession Number  
209511

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209511**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209511

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by an applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

# **INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 448.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
04 April 1997

Accession Number  
97975

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 97975**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97975

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 448.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209081

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209081**

### **CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

### **NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

### **AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

### **FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209081

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 454.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
04 April 1997

Accession Number  
97976

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 97976**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97976

## UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 455.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
04 April 1997

Accession Number  
97977

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 97977****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97977

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by an applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 455.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209082

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209082**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209082

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 457.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
06 January 1998

Accession Number  
209568

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209568**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.



ATCC Deposit No.: 209568

## UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 458.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
07 April 1998

Accession Number  
209746

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available, until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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| Authorized officer  |                               |  | Authorized officer   |                                   |  |

**ATCC Deposit No. 209746**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209746

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 461.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
28 April 1997

Accession Number  
209007

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209007**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209007

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 461.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209083

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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**ATCC Deposit No. 209083**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209083

#### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 465.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
18 May 1998

Accession Number  
209877

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

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**ATCC Deposit No. 209877**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: 209877**

## **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
28 April 1997

Accession Number  
209008

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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**ATCC Deposit No. 209008**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209008

#### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209084

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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**ATCC Deposit No. 209084**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: 209084**

### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

# **INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
28 April 1997

Accession Number  
209010

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209010****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209010

#### **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 466.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
29 May 1997

Accession Number  
209085

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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**ATCC Deposit No. 209085**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.



**ATCC Deposit No.: 209085**

## **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 469.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
28 April 1997

Accession Number  
209009

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 209009

#### CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

#### NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

#### AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

#### FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: 209009**

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 475.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
28 April 1997

Accession Number  
209011

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**ATCC Deposit No. 209011**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

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ATCC Deposit No.: 209011

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

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#### SWEDEN

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#### NETHERLANDS

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*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;
  - (f) a polynucleotide which is a variant of SEQ ID NO:X;
  - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
  - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
  - (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.
2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.



3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence  
5 included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to  
10 SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.  
15
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.  
20
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.  
25
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.  
30
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

5 (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence  
10 included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

15 (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

20 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

25 15. A method of making an isolated polypeptide comprising:  
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

30 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

- 5 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
  - (b) diagnosing a pathological condition or a susceptibility to a
- 10 pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
- (a) determining the presence or amount of expression of the
- 15 polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

- 20 20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:
- (a) contacting the polypeptide of claim 11 with a binding partner; and
  - (b) determining whether the binding partner effects an activity of the
- polypeptide.

- 25 21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay,
- 30 wherein the method comprises:
- (a) expressing SEQ ID NO:X in a cell;
  - (b) isolating the supernatant;

- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

1/10  
Figure 1A

1 AATTCGGCACGAGGGAAATTCAAGCACTTTTCTAAAGAAGGGGAATGGATGCTGAAA 60

61 CAACACGThTCCCACAAAGGGAGCAGACACTGGGCTTGTGAAGCTGCCCCATACCTTCCC 120

121 CACAGAACTGGGGTCCGGCTCCCTGACATGCAGATTTCCACCCAGAAGACAGAGAAGGA 180

181 GCCAGTGGTCATGGAATGGGCTGGGGTCAAAGACTGGGTGCCTGGGAGCTGAGGCAGCCA 240

241 CCGTTTCAGCCTGGCCAGCCCTCTGGACCCCGAGGTTGGACCCTACTGTGACACACCTAC 300

301 CATGCGGACACTCTTCAACCTCCTCTGGCTTGCCCTGGCCTGCAGCCCTGTTCACTAC 360

1 M R T L F N L L W L A L A C S P V H T T 20

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21 L S K S D A K K A A S K T L L E K S Q F 40

421 TTCAGATAAGCCGTGCAAGACCGGGTTTGGTGGTGACGGACCTCAAAGCTGAGAGTGT 480

41 S D K P V Q D R G L V V T D L K A E S V 60

481 GGTTCCTTGAGCATCGCAGCTACTGCTCGGCAAAGGCCCGGgaCAGACACTTTGCTGGGGa 540

61 V L E H R S Y C S A K A R D R H F A G D 80

541 TGTACTGGGCTATGTCACTCCATGGAACAGCCATGGCTACGATGTCACCAAGGTCTTTGG 600

81 V L G Y V T P W N S H G Y D V T K V F G 100

601 GAGCAAGTTCACACAGATCTCACCCTCTGGCTGCAGCTGAAGAGACGTGGCCGTGAGAT 660

101 S K F T Q I S P V W L Q L K R R G R E M 120

661 GTTTGAGGTCACGGGCCTCCACGACGTGGACCAAGGGTGGATGCGAGCTGTCAGGAAGCA 720

121 F E V T G L H D V D Q G W M R A V R K H 140

721 TGCCAAGGGCCTGCACATAGTGCCTCGGCTCCTGTTTGAGGACTGGACTTACGATGATT 780

141 A K G L H I V P R L L F E D W T Y D D F 160

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Figure 2

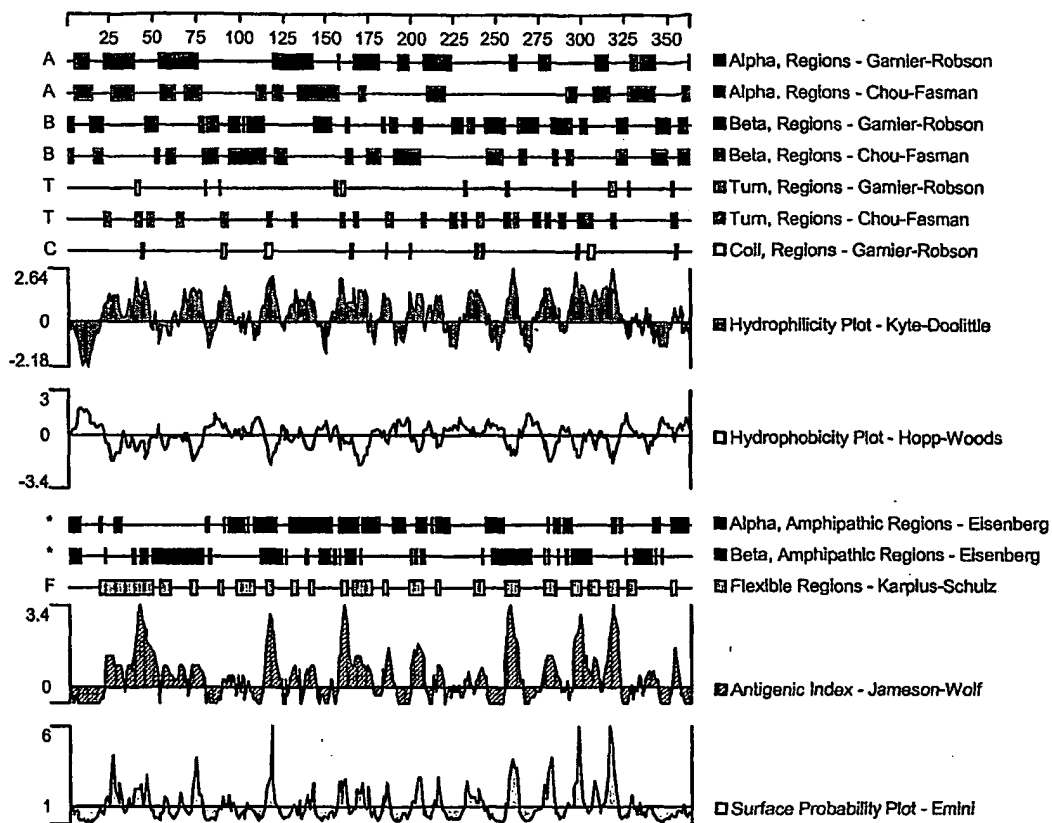


Figure 3A

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241 AGGAGCAGGATTTGGAGCTGGGAACCTGCGCTCCACTCGACGAGGCCATCAGCTCCACAG 300  
34 E Q D L E L G T L A P L D E A I S S T V 53  
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54 W S S P D M L A S Q D S Q P W T S D E T 73  
361 CAGTGGTGGCTGGTGGCACCGTGGTGTCAAGTGCCAAGTGAAAGATCAGGAGACTCAT 420  
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421 CCCTGCAATGGTCTAACCCTGCTCAGCAGACTCTCTACTTTGGGGAGAAGAGAGCCCTTC 480  
94 L Q W S N P A Q Q T L Y F G E K R A L R 113  
481 GAGATAATCGAATTCAGCTGGTTACCTCTACGCCCCACGAGCTCAGCATCAGCATCAGCA 540  
114 D N R I Q L V T S T P H E L S I S I S N 133  
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194 A A R L T W R K G D Q E L H G E P T R I 213  
781 TACAGGAAGATCCCAATGGTAAACCTTCACTGTGCTCAGCAGCTCGGTGACATTCCAGGTTA 840  
214 Q E D P N G K T F T V S S S V T F Q V T 233  
841 CCCGGGAGGATGATGGGGCGAGCATCGTGTGCTCTGTGAACCATGAATCTCTAAAGGGAG 900  
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Figure 3B

901 CTGACAGATCCACCTCTCAACGCATTGAAGTTTATACACACCAACTGCGATGATTAGGC 960  
254 D R S T S Q R I E V L Y T P T A M I R P 273

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394 G T Y L T H E A K G S D D A P D A D T A 413

1381 CCATCATCAATGCAGAAGGCGGGCAGTCAGGAGGGGACGACAAGAAGGAATATTTTCATCT 1440  
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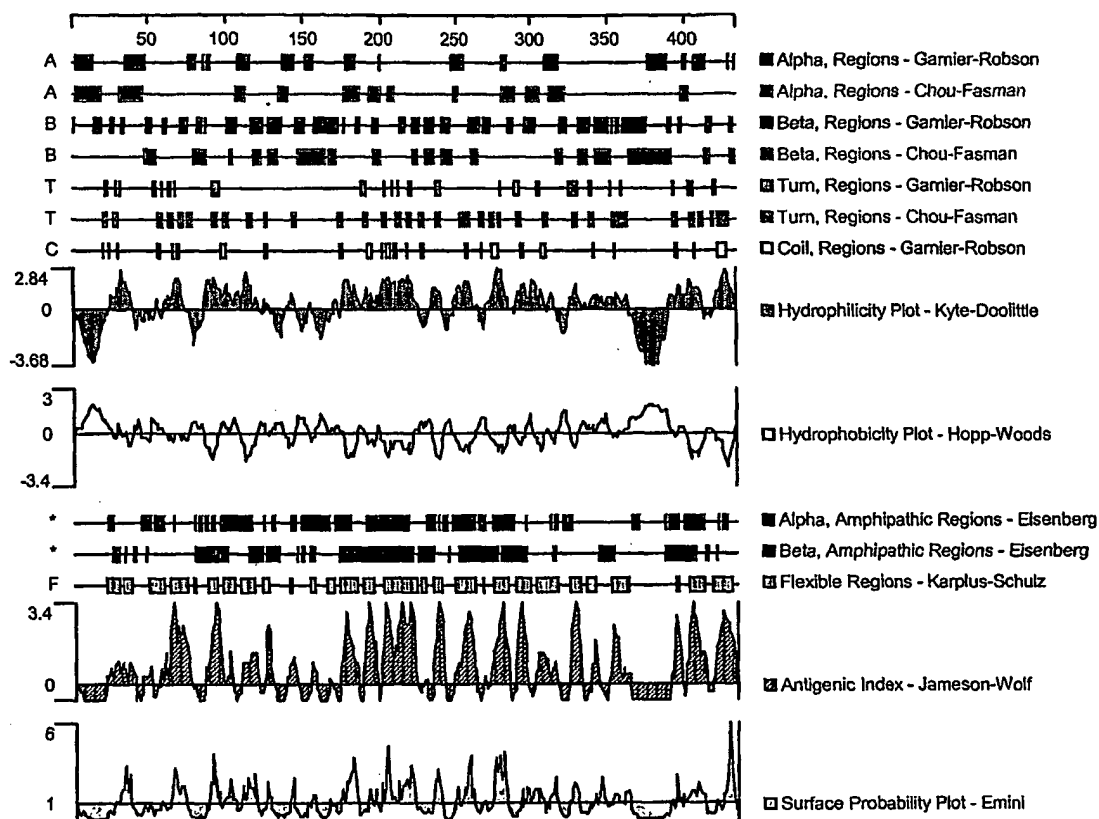
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## Figure 3C

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1981 ACACCTGAGCACTACGGACAGGGAGGCAGGTGCCACCTTGACACCTCTCTTCCATAGCAA 2040  
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2161 TGGAGAGGAAGGATGGAGGTGGACTCTCACCCCATTCCTCCCGGAAATGAACAAAGCCGG 2220  
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2461 AGCCCTTCATCCTTCCCTCCCTCAGCAGCCAGGCAGACATAACAACAAACTACTAAAAGG 2520  
2521 AAAAAAAAAAAAAAAAAA 2537

Figure 4



## Figure 5A

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121 AGATCACCG CGACTCAAC CTCTGCAGG TCTCGGAGCC CTGGAGCCA TGTGTGAGAT 180  
37 E I T R D F N L L Q V S E P S E P C V R 56

181 ACCTGCCCAG GCTGTACCTG GACATACACA ATTACTGTGT GCTGGACAAG CTGCGGGACT 240  
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301 GGAAGCTGTA CACCATCATG AACTGTTCT GCAGGAGAGA TTGGTATT CTTGTGGATG 360  
97 R K L Y T I M N S F C R R D L V F L L D 116

361 ACTGCAATGC CTGGAATAC CCAATCCCAG TGACTACGGT CCTGCCAGAT CGTCAGCGCT 420  
117 D C N A L E Y P I P V T T V L P D R Q R 136

421 AAGGGAAGT AGACCAGAGA AAGAACCCTA GAGAACTAAA GTTATGTCAG CTACCCAGAC 480

## Figure 5B

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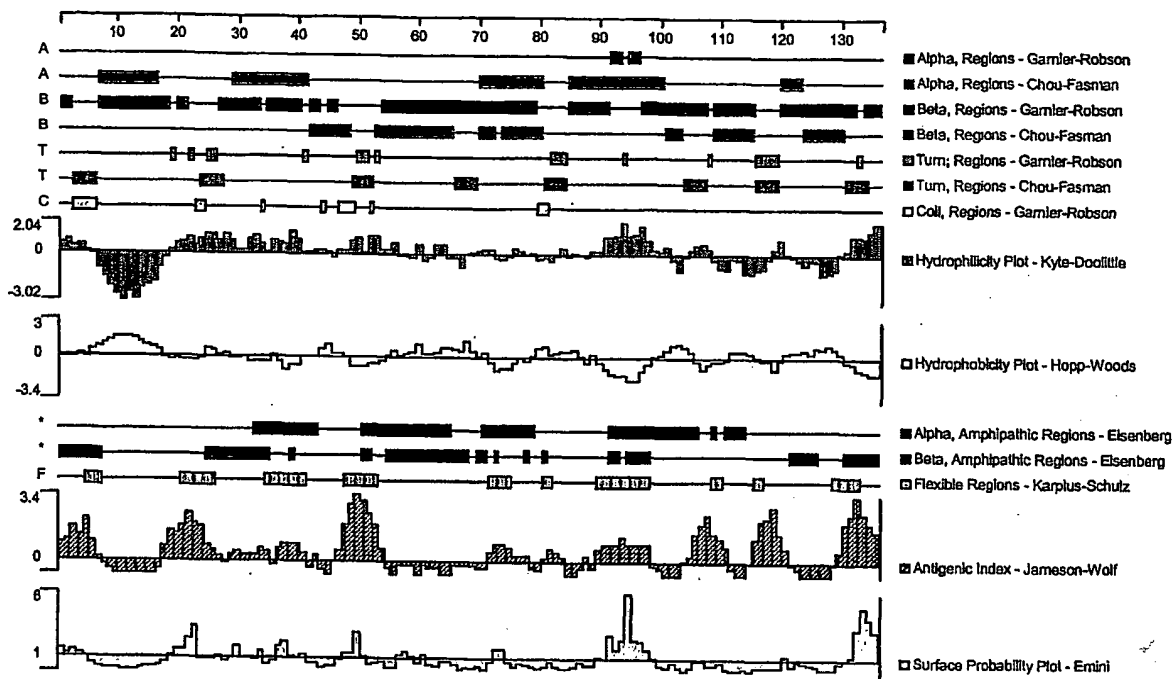
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Figure 6



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| aagtacatct  | tgaattttgg | gggggcatct | ctgattttaa | aaaagaaaaa  | ggctgcttga | 2160 |
| tgtatgttat  | gcagagacac | tctgcctctg | gtggctgcag | agcaataccc  | aagcctcatt | 2220 |
| tgggaaggctc | aacatttgga | attgcacttt | aattgattaa | tcctcaattc  | atgtggcctt | 2280 |
| acgggatggt  | gggtctggga | ccccaattca | ttcttatctg | ccaaagaatt  | atctagaagc | 2340 |
| acatcaaata  | ccagcaccac | acctgcacaa | tgggggtgga | aaacttttgt  | atccctaagc | 2400 |
| atattatttt  | atagtgtctg | ccatgccatg | tggaataact | ttatttttaa  | cctcaggatt | 2460 |
| taaataaagt  | aaacactatg | acatttaaaa | aaaaaaaaaa | aaaactcgag  | ggggggcccg | 2520 |
| taccca      |            |            |            |             |            | 2526 |

&lt;210&gt; 12

&lt;211&gt; 1131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (839)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 12

|            |            |            |             |            |             |      |
|------------|------------|------------|-------------|------------|-------------|------|
| cactgcacca | gctttgttat | ctgtaaaatg | atgataatac  | caacaccttc | ttcttggggg  | 60   |
| actgaagatg | agagaacatg | atatgtgtaa | agtgccttcc  | acaataccca | gaacatagca  | 120  |
| aacatgtaat | gaatgtagta | atagtaatta | ttttattttc  | ttttgattca | gttgggacta  | 180  |
| tgttcagctg | taacagaata | cccaaaaata | ctgtttttaa  | caaattaaag | tttwgttggtg | 240  |
| aagttttggt | acgaattcag | acaatccagg | gcttttatag  | atgcaccagg | atcagcaggt  | 300  |
| acaaaggcat | ctttcctgat | ttctgccagt | ctcaatgcat  | gggttgcaat | ccagartcca  | 360  |
| rgatggcagt | tccagccctg | gttacgccca | tattagcaca  | cagaaagaaa | gagaaaggga  | 420  |
| tgtgcctctt | cactttaatc | atagctcca  | ctagatgcac  | ccactacttc | tgtgatact   | 480  |
| ccattagcta | atgcttgctt | acatggtcac | acttagtttc  | cagagagaca | tgtctggaca  | 540  |
| gtcatgtgct | caattaatat | ccaagtgtcc | aattactgag  | aaaaaaagaa | actagcacct  | 600  |
| ttgcttggtt | gcattcctct | tagcataagc | cacattcttt  | ttatgaagtt | gtcctcagtt  | 660  |
| acttggatgc | ctcagttgtc | ctttcawtta | gaaawgcycc  | tkggacaycc | tgaawctgac  | 720  |
| ttcttttgtc | atcagcacca | tcactaccac | tgccytcttc  | aaagccacca | cgttctgtcc  | 780  |
| ccaggatggt | tgaacaacc  | accataggga | ctttttgcct  | tctacttcca | cacaatagnc  | 840  |
| cagagtaagc | ttttgaaaat | gtaggtcaga | tcagtctctc  | ctcttctctc | tcaaaacctc  | 900  |
| cccgatggct | tttcatatta | ctcaaaagaa | aacctaaaac  | tttgctgtga | gatctatgtg  | 960  |
| accgggctta | ttcttctctc | tactttatct | ctgtattgct  | cttctcactc | ctactccagc  | 1020 |
| catcccacct | ccttgctgct | tgtcctatac | tcctaaaaga  | agttcagttc | tcctttatga  | 1080 |
| tatttgcact | taaaatagaa | aaaaaaaaaa | aaaaaaaaact | cgaggggggg | c           | 1131 |

&lt;210&gt; 13

&lt;211&gt; 941

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| ggcacgagta | gcatttccatt | taatctgcag | gtatattctc | ccaacagttt | attgtcatgt | 60  |
| gatgtcctca | gccaaagattg | traggcagag | aggagctgtc | ccaacctact | ataccaccga | 120 |
| ggctggagag | atcatatttt  | tggtattaaa | ctggagtctc | tccatccttc | acattgttga | 180 |
| tgtcctctgt | agcaaaccgg  | aaaagtccag | gcagaagat  | gccgctagcg | gtttgagcca | 240 |
| gagaatgaca | gctctggttt  | ggagaaaagg | gccggatggt | ggctctagaa | agcccatcct | 300 |

|            |            |            |            |             |             |     |
|------------|------------|------------|------------|-------------|-------------|-----|
| tctgctcttc | ttttttctcc | cccttatatt | gtgctttcat | tcattcattc  | attcatcaaa  | 360 |
| catttggtga | gcacctatta | tgtgtcaagc | tctgtgctag | cctctggaaa  | acctgcccctc | 420 |
| atgtagctca | ctgtggagta | ggagaaacaa | tgactacact | atgataagca  | cgggttggtca | 480 |
| gggtctcaca | gagcagtggc | ccctcatcca | gaccgatgag | gtcaaagaag  | gcatccaggc  | 540 |
| gaggatggtg | tcagagctaa | ctgaagaatg | agagggagct | gcaccascag  | gggttggaac  | 600 |
| tgaaggtggc | agtgcctgga | gtcttgattc | cagcagaggg | agagcagtct  | gtgaaaaggc  | 660 |
| accaagggtg | ggagagggca | gagcacatgg | aggaacttca | ggtagtctctg | gatggcsctg  | 720 |
| gggcaaagct | agagaggtaa | gaagaatcta | caaagtgtcc | tcgagttaca  | tgaacttcca  | 780 |
| tccaataaaa | cccattggaa | acgaaaaatt | taagtcagaa | gtgcatttaa  | ggctgggtccg | 840 |
| agtagaatga | tttttacaac | gaattgatca | caaccagtta | cagatgtctt  | tgttccttct  | 900 |
| ccaactccac | tgcttcacct | gactagcctt | taaaaaaaaa | a           |             | 941 |

&lt;210&gt; 14

&lt;211&gt; 843

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (525)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 14

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| cnagggataa | ccccaaagnt  | gggaaataaa | ccctcaatta | aagggggaac | caaaaagctg | 60  |
| ggaagtccc  | ccccgcggtg  | gcggccngnt | ctaggaacta | gtggaatccc | ccggggctgc | 120 |
| agggaattcg | gcacggagtg  | ggaatgttgt | ttgtatgata | ctatttccac | aawatgcatt | 180 |
| gagacttggg | ktgtggccta  | ggacatgggc | aattcttctt | aaatattccg | tgaatttctt | 240 |
| tagtgcata  | tctccgatgg  | gggtgtggg  | gacagagttc | taaatatgcc | cattagatta | 300 |
| aatctcttca | ttctgttgct  | cacatcttct | atatccttat | taatctgtca | atctcttcaa | 360 |
| gagaggtggt | attaaaatct  | ctcactgtat | gtgtcacttt | gcccttaaaa | ttctgatgat | 420 |
| ttgctttata | aatggttata  | accattttcc | aggaagaaca | ttaaagaact | ttccattggc | 480 |
| attatccagt | ttccctcaaa  | atactgggtt | tttttatatt | ggctnctaag | cagctatgaa | 540 |
| tccagtttct | cagaagccct  | tgtctcaagg | catttgtttc | cagattacct | tgtagcatc  | 600 |
| cacactatgg | gctatttttag | aaaaacaaaa | aaagtatcaa | aatcatatag | ctatgatttt | 660 |
| cctgtgcttg | aaggagcctt  | aaagctcatc | tagtccagcc | agtatttggt | catccaaatt | 720 |
| ctgccaagaa | atctctattg  | tcaagatatt | ctttaccatc | tttgggacat | tctcattatt | 780 |
| agaaacaaat | cctaagaaga  | aattctgcca | takacaaccc | atccgttctt | taaaaaaaaa | 840 |

aaa

843

<210> 15  
 <211> 1018  
 <212> DNA  
 <213> Homo sapiens

<400> 15  
 ctgtaatttt taattttcat ataccgtgct ttgattctaa ttttattttt tgagttctct 60  
 gaaggttaca tatacagagt gcttcaggaa tgatcatttt gttattattc atgcttctta 120  
 acaatgttgt tttagtccaa gaagataatt gccagagaaa gaatacagtg caggaaagaa 180  
 gargctggag ccagtgtga agarggattg agargacaga cattgtggga atgaaatcat 240  
 gaataatcgt gtttttgaat tgtccaaaaa cttctacaaa ccatgaaatg ttggagttta 300  
 aatctaattg ttgaaaaatt cccacattc cttgtatccc ttaggttgag cataattcca 360  
 catccgtgga ctgatgcaact tcccagagg gggcctcatt aactcttccg aggcagcagc 420  
 agcaagggca cccctcctt tccccccaca ccccayttct catggctctt ctttctctca 480  
 tctcatgtct aggttagaaa agggcacaag gtaaggaagc ccttggaat aggcgaatc 540  
 tggctatcta atttgtgcc aaataactta tgtgcttgaa tttaaaaaca gcaaacatgt 600  
 agaaaggtaa ttataattat gaggccagtt ctttaagcta gctttttttc ccctctcaa 660  
 cagcatattg gcttggatgt cagcaggaga aagtgttttt tgcaatacac ataatgcata 720  
 tatgtcctg ttagcaatct atagaaaata gatattgctc attaaggtaa atatttttgt 780  
 tgatgaatga tctggaatgg tctggacttg ttgtgtgaac aggaaattgc tctgtaggct 840  
 ttgacttggt aggtaaagag tgaggctggt aagattaatt aaagtaaata ctgtgacaat 900  
 aggatgtcaa aaccaaaaac gtgtttctga aactcaagga attaatgaca catagggaag 960  
 tttttgccat attaagcata gagtaggaga ggcaagtcaa gaataaaaaa aaaaaaaa 1018

<210> 16  
 <211> 661  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (25)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (478)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (661)  
 <223> n equals a,t,g, or c

<400> 16  
 tttaagaaat tagtgaatcc ccgntgcag ggaattcggc acgaggagga ggccgtcagc 60  
 tggcaggagc gcaggatggc agctgytccc cggggttgca cccccccagy tctgtctggac 120  
 ataagytggt taacagagag cctgggagct gggcagcctg tacctgtgga gtgccggcac 180  
 cgcttgaggg tggctgggcc aaggaagggg cctctgagcc cagcatggat gcctgcctat 240  
 gcctgccagc gccctacgcc cctcacacac cacaacactg gcctmtccga gctgtctggag 300  
 catggagtgt gtgaggaggt ggagagagtt cggcgctcag agaggtaacca gaccatgaag 360  
 gtgcgcaggg cagggtcgg acctaccca ggaatgtcct gccctgggaa tgacaacaca 420  
 gtccacacca tgcacgggga ggcaaacagg ggcagctgac ccagcccagg ggtcaganga 480  
 ggtcttgccg aggaagtggc agctaagctg atacctgata tgcacwagkc agccargygg 540

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| agacaggcaa | ggaagaagct | tgttttgagg | acagaatddd | ctagatcact | cagcaccatc | 600 |
| tggcttttgg | ggctttttgt | tttattttgt | ttttgagacg | gggtctcgct | ctgtcgccca | 660 |
| n          |            |            |            |            |            | 661 |

<210> 17  
 <211> 553  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (507)  
 <223> n equals a,t,g, or c

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| <400> 17   |            |            |            |            |             |     |
| ggcacagggc | tatttgcccc | tctctccaca | tgacagaact | gctctaagtt | tctttgctgc  | 60  |
| tcttctcagc | tgtcagacgg | cttgctgctt | gttttccaca | ccaccatgtc | tattctttgc  | 120 |
| tgtccttwac | tctgcctggt | tttttccttt | tgtatttctt | ctggctcttg | tcccttttcc  | 180 |
| cacgtgtcwc | agctttcctt | tattgccact | ttcagtcaga | gcagtcctgt | gcttctgggtg | 240 |
| ccggcataca | atacttactt | gagtttcttg | gcttttcttg | actgtgcac  | tcttacttca  | 300 |
| acataggaat | agcctgtcat | agaatttctc | cagttccagg | gctcaagagg | gagagtgcc   | 360 |
| gaaaattgag | actgttttcc | ctgtcttgga | ttgaattcat | aaagcaaac  | cagtgtttgt  | 420 |
| gtgaggggtt | gctgtgtcat | gcctataggt | tgtttgggtg | caaacctata | gaatccagcc  | 480 |
| tgcgaaaaga | aagraaccag | agaatanacg | catcagaaca | atgcttgaca | tcatttctca  | 540 |
| atcaagcagt | cca        |            |            |            |             | 553 |

<210> 18  
 <211> 869  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (635)  
 <223> n equals a,t,g, or c

|            |             |            |             |            |             |     |
|------------|-------------|------------|-------------|------------|-------------|-----|
| <400> 18   |             |            |             |            |             |     |
| ggcacgagct | gccaacactg  | aggtcttcgt | ggcttctcac  | atctagatgt | atccctctca  | 60  |
| aatctatcct | ctatccaggc  | accagattga | ggatatctaaa | atgtcaactt | tccagttact  | 120 |
| ccttcttata | ctagcccaat  | caacttacaa | gataaagtcc  | aagccccttc | atatgacaaa  | 180 |
| ccacaccctg | cttaactctc  | caggtttgaa | tccttcatct  | cctactttaa | actttaaaac  | 240 |
| ccagcagcac | gaaagtgtct  | cctatgcatg | ttgccatatg  | cgttctctcc | atcatgcatt  | 300 |
| tgcctgagca | agatgtcttg  | agttaacatc | ttattcttta  | agactcattg | tggtagtaga  | 360 |
| cagcctttta | taacggatcc  | ttggccaggc | acagtgactc  | acacctgtaa | tcccagaact  | 420 |
| ttgaaaggcc | aaagaaggaa  | gaaagcttga | ggccagtagt  | ttgagaccag | cctgggaaac  | 480 |
| agagagatat | cccactctgta | ccaaaaattd | aaaaaaatat  | tagcagggag | tagtgggcatg | 540 |
| cacaagtggg | cccagctcca  | tgggagastg | aggtaggaac  | atcacttgag | cccaggaagt  | 600 |
| caaggctgca | gtgaaccatg  | atcagaacat | tgcantccag  | cttgggtaac | agagtggagac | 660 |
| cttaggtcag | aaaaatgaat  | aaataagcat | aaaattttta  | aaacttagcc | aggcatggtg  | 720 |
| gcacacatct | gtggtccctg  | ctacttagga | ggctgaggtg  | agaggatcct | tgagcccagg  | 780 |
| aggtaaacac | tacagtggac  | tatgattgtg | ccactaaact  | ccaacctggg | tgaaaaagca  | 840 |
| aaaccctgcc | aaaaaaaaaa  | aaaaaaact  |             |            |             | 869 |

<210> 19  
 <211> 959

<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (930)  
<223> n equals a,t,g, or c

<400> 19  
ggcgagccga gatcgtgccca ttgcactcca gcctggggcaa caagagtga actctgtctc 60  
aaaaaaaaaa aattataata ctatatgccca taaaatgaca ttccatattt aaagagtttt 120  
ttaaaactct tgtattcaca tgccataatt tgaaacccta ttccactgaa tgagaatggt 180  
atctgttgct ctcatTTTTT catttttattc cttaacaatt tccaccacag ccagtgcata 240  
taatggcaat gacaccacag gatggaatga taagtcccat crcmgctcag tcaagacgca 300  
gacttgatgt gggcccaaca acagtcaata atggagtctc caaaataaag ctctatagga 360  
aaggtaaata cccgctgcac aagaaaccac agcatctagg ttctaaccoc atctctatga 420  
agagcttgct gggagagttt tgacattwaa caatctgtct gatkgccaat ttttctctc 480  
tataaaatga taatgttkga ytcaaagatc caaagtcaat tcatgggtcta aaacttaatg 540  
atttttttag gttttgkgac atttactgt acactgtagt aatttatatc ttattttccc 600  
actaattag aaaaatatytt aaatgatcct taattggcaa tgggtcctaa gaattttggt 660  
ttaaatccct gttacccaaa agagcccttt tttgtatctc gcagtagtta caaggatctt 720  
tctaaatctt aaaaaaaaaa aaaaaagaaa gaaagaaaag aaaagaaaaa agtcagccg 780  
ggcgtgggtg ctcatgcctg taatcccagc actttgggac caagggtggac agatcacgag 840  
gtcaggagat ggagaccatc ccggccaaca tggagaaacc ctgtctctac taaaaaaaaa 900  
aaaactcga gggggggccc gtacccaatn cgccggctag tggctgtaaa acaatcaaa 959

<210> 20  
<211> 1446  
<212> DNA  
<213> Homo sapiens

<400> 20  
cggggcaggg ctgtgtggca ccgccagggg gcggggccac ctgagtcact ttattgggtt 60  
cagtcaacac tttcttgctc cctgttttct cttctgtggg atgatctcag atgcaggggc 120  
tggttttggg gttttcctgc ttgtgccaag ggctggacac tgctgggggg ctggaaagcc 180  
cctcccttcc tgtccttctg tggcctccat cccctcatgg gtgctgccat ccttcttgga 240  
gagagggagg tgaaagctgg tgtgagccca gtgggttccc gccactcac ccaggagctg 300  
gctggggccag gaccgggaga gggagcactg ctgcccctct ggcctgctc ctcccgagt 360  
taagggtgga ccgagcctcg ctttccccac tgttctggag ggaaggggaa ggagggggtc 420  
ttcaggctgg agccaggctg ggggtgctgg gtggagagat gagatttagg ggggtcctca 480  
tggggtgggc aggcctgggg tgaaatraga aaggccaga acgtgcaggt ctgaggagg 540  
gaagtgtcct gagtgaagga ggggaccccc atcctggggg atgctgggag tgagttagtg 600  
agatggctga gtgaggggta tggggagcct gaggttttat gggcctgtgt atccccctt 660  
cccggcccca gcctgcctcc ctccctgccg cctggcccac aggtctccct ctggtccctg 720  
tccctctggt ggttggggat ggagcggcag caagggtgt aatggggctg ggttctgtct 780  
tctacaggcc accccgaggt cctcagtgtg tgctggggga gccggacggg gctcctgagg 840  
ggtacaggtt ggttggggcc tccctgaggg tctggggtea ggtttggct ctgctgctc 900  
tcagtcacca agtcaacctc ctctgaaaat ccagtcctt ctttgatgt ccttgtagt 960  
cactctgggc ctggctgtcg tccctcctca gcttctgtt cctgggacaa ggggtcaagcc 1020  
aggatgggccc caggcctggg atccccacc ccaggacccc caggccccc cccctgctgc 1080  
tttgccgggg gcagggcaga aatggactcc ttttgggtcc ccgaggtggg gtccctccc 1140  
agccctgcat cctccgtgcc stagacctgc tccccagagg aggggccttg acccacagga 1200  
cgtgtgggtg gcctggcac tcagggaccc ccagctgccc cagccctggg ctctggcgca 1260  
tctcttccct ctgtcccgga agatctgcgc ctctagtccc ttttgagggg ttcccatcat 1320  
ccctccctga tattgtattg aaaatattat gcacactgtt catgttcta ctaatcaata 1380  
aacgctttat ttaaagccaa aaaaaaaaaa aaaaaactcg agggggggcc cgtacccaat 1440  
tcgcca 1446

<210> 21  
 <211> 1471  
 <212> DNA  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (1470)  
 <223> n equals a,t,g, or c

<400> 21  
 caaaaaataa taatgataat ttaaaaataaa taagtaacta ataaaaagat tttatatccc 60  
 agtcttatga tgttggttg caaggctaga taaaaagatg ttagaatgaa agaacadatt 120  
 tttagtata tgtaaatgaa ggattctaca atagtcatat atttttatat gaatgaatgt 180  
 tgggttgggc tggagaggta tgtgtgtgta aatataaagg tctcacattc agagtatagc 240  
 tctgaaataa tggaaactcat gtctacaatt caacatgcat ctgtatagtt acatctcatg 300  
 taaatataca cagacatatt ttgcagccag taattgacag ttaatgtcca aaacagggtga 360  
 ttgataggta acagaaatta gataaccacc aattttgccc aagagaaaga ctagaaggac 420  
 taaaagcagt tgaatgtatg gtactgacat tgtcataagc agtctgataa ccagtttatt 480  
 gaaacgtgtg cattaacaga gaatttaatt ttaaaccat aattttctct atccattaaa 540  
 atattataat tgtagtagt atgaaaccaa caggaaatgt tttttaatca tttagttagg 600  
 tgattcattt gtttcatggg caaacactat ccaggaaaag ccttgcttgc ctgtttccca 660  
 aagagctcta agaaatagaa tcaagtgtaa aatggttcag accattcagg atttcttgtc 720  
 actcttctca accccgatct tcctgttatt actgatgttt gaaaccctgt cattagcccc 780  
 ggcttggtta aagccctca ggtcacctc tcattcatag caatagaatt caaccccaag 840  
 tgggtgatgg tgtcccagc acagccgaga gacctgatct ctggattcag tgcttttagc 900  
 tcttcgagtt taccctaaga taccttcggg caatattttt aaccaaccca aaagctcttc 960  
 aggtcatttc tgaagaggac aagggtgaatc ttggcttgga acaccatttt tgggctcttg 1020  
 ctactgaatg aatcagaaag gaattttttc tgaagagcat tagaaagtaa aggagatgtt 1080  
 aaaataagtt cttgaagtat gttttatatt tatctaaaac actgatttta aaagtttaca 1140  
 ttcaaatgtg tattcaaaaag aagtactgat ttgtaattat tatagtttgt gtgtatcatc 1200  
 cccttttaac cgtgcctaac aactgtactt aaattttgtt ttctagtgt aacaaatgtt 1260  
 tcccataaga ttttctagag ccaaataatg ggagtgaata attccttaag tggtatataa 1320  
 gaaaatataat tagaaaatca gctttggatt atacgatttc taaaatatac taatacagaa 1380  
 tcctcagtaa tatgttttga attggatttt ttctcagaac tggtacataa taaataatac 1440  
 atcaaccaga aaaaaaaaaa aaaaaaattt c 1471

<210> 22  
 <211> 1402  
 <212> DNA  
 <213> Homo sapiens

<400> 22  
 agggacgtct tgcctgagga gatgccatt tctgtcctgg rttaccctca ctgcgtggtg 60  
 catgagctgc cagagctgac ggcggagagt ttggaagcag gtgacagtaa ccaattttgc 120  
 tggaggaacc tcttttcttg tatcaatctg cttcggatct tgaacaagct gacaaagtgg 180  
 aagcattcaa ggacaatgat gctggtggtg ttcaagtcag ccccatctt gaagcgggac 240  
 ctaaaaggta aacaagccat gatgcagctc tatgtgtgta agctgctcaa ggtacagacc 300  
 aaatacttgg ggcggcagtg gcgaaagagc aacatgaaga ccatgtctgc catctaccag 360  
 aagggtgcggc atcggctgaa cgacgactgg gcatacggca atgatcttga tgcccgccct 420  
 tgggacttcc aggcagagga gtgtgccctt cgtgccaca ttgaacgctt caacgcccgg 480  
 cgctatgacc gggcccacag caaccctgac ttctgccag tggacaactg cctgcagagt 540  
 gtcctggggc aacgggtgga cctccctgag gactttcaga tgaactatga cctctggtta 600  
 gaaagggagg tcttctccaa gccatttcc tgggaagagc tgctgcagtg aggtgttgg 660  
 ttaggggact gaaatggaga gaaaagatga tctgaaggta cctgtgggac tgtcctagtt 720

|             |            |            |             |            |            |      |
|-------------|------------|------------|-------------|------------|------------|------|
| cattgctgca  | gtgctcccat | ccccaccag  | gtggcagcac  | agccccactg | tgtcttccgc | 780  |
| agtctgtcct  | gggcttgggt | gagcccagct | tgacctcccc  | ttgggtccca | gggtcctgct | 840  |
| ccgaagcagt  | catctctgcc | tgagatccat | tcttccctta  | mttcccccam | cctcctctct | 900  |
| tggatatggg  | tggttttggc | tcatttcaca | atcagcccaa  | ggytgggaaa | gctggaatgg | 960  |
| gatgggaacc  | cctccgccgt | gcattctaat | ttcaggggtc  | atgctgatgc | ctctcgagac | 1020 |
| atacaaacc   | ttgcctttgt | cagcttgcaa | aggaggagag  | tttaggatta | gggccagggc | 1080 |
| cagaaagtgc  | gtatcttggg | tgtgctctgg | gggtgggggtg | gggtgtttct | gatgttattc | 1140 |
| cagcctcctg  | ctacattata | tccagaagta | attgctggag  | ctccttcagc | tgcttcagca | 1200 |
| ctttgatttt  | ggacagggac | aaggtaggaa | gagaagcttc  | ccttaaccag | aggggccatt | 1260 |
| tttccttttg  | gctttcgagg | gcctgtaaat | atctatatat  | aattctgtgt | gtattctgtg | 1320 |
| tcattgttgg  | gtttttaatg | tgattgtgta | ttctgtttac  | attaaaaaga | agcaaaaata | 1380 |
| ataaaaaaaaa | aaaaaaaaaa | ct         |             |            |            | 1402 |

<210> 23  
 <211> 1047  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (301)  
 <223> n equals a,t,g, or c

|            |            |            |            |            |             |      |
|------------|------------|------------|------------|------------|-------------|------|
| <400> 23   |            |            |            |            |             |      |
| ggcacagggg | actacaggca | cccacgacca | taccagcta  | atTTTTgtat | TTTTTttag   | 60   |
| agatgggggt | tcacgatgtc | gcccaggctg | gtcttgaact | cctgggcttg | agcgatcttc  | 120  |
| ccatctttcc | atcttggcct | cctaaagtgc | tgggactgca | ggcatgagcc | accatgcca   | 180  |
| gccaagattc | ttattgatta | ccatgttgct | tcaagaagcc | aagccagttt | ccaatattcc  | 240  |
| ccatttgctg | gagtccttgg | actttgggta | gaagcaactg | gtaaattgtt | aattggaaca  | 300  |
| nttgggtggg | tagataacca | cgtatggcca | aacctagagc | atctaggctc | acaattacta  | 360  |
| tcctgacttg | ataacaagtg | ttctgatatt | aacctgaaaa | tgggaataat | gccaaatctg  | 420  |
| tgtaacttaa | catctatata | cacagtgggg | agaactgaag | ttattaaacc | tggaatctct  | 480  |
| gtgatcaagg | ctaacagtag | ttatctaaga | agcaaaggac | ctacaattct | tagacttgga  | 540  |
| gtcatattct | ttaaggacgt | gttctgaaac | tatatcaagc | atctgggttc | cacgtatttc  | 600  |
| tccttcagaa | attatgaagt | acaagtaaaa | atgaaggtag | agggtaagac | acatgctgct  | 660  |
| ttcttgctct | tgagtggaga | cagttttcca | gccatcttaa | ccccttwaca | caaaacaatt  | 720  |
| tgtgttttat | agcaataaag | tgactcaaca | taatttcaat | atgatgttta | tccaccagta  | 780  |
| ctttcctttc | agcttctagt | cccataartg | gtttgtgaag | tcacggttta | cattagccaa  | 840  |
| gataggccta | gacttgaagt | ctagaatgtt | tttcccacta | tatgccaaag | tagaatgtgg  | 900  |
| gtatctcagg | gtcatttttg | ttgttcaatt | tcccacctgt | acagttgtta | tgattcactt  | 960  |
| tccttatgtg | tctaataaat | cttgttccat | gaaatgatca | aaaaaaaaa  | aaaaaaaaact | 1020 |
| cgaagggggg | cccgttacc  | aatcgc     |            |            |             | 1047 |

<210> 24  
 <211> 990  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (834)  
 <223> n equals a,t,g, or c

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 24   |            |            |            |            |            |     |
| ttggaaaggg | tctagctctt | tctcattcac | caactatatt | agaagcactt | gagggaaatt | 60  |
| taccactcca | aatccaaagc | aatgaacagt | cttttctgga | tgattttatt | gcctgtgtcc | 120 |



|             |             |             |            |             |            |     |
|-------------|-------------|-------------|------------|-------------|------------|-----|
| caggatcaag  | tgggtggaagg | cttgcaagggt | ggcttcagcc | agattcatat  | gaggatcctc | 180 |
| agaaaacatc  | tttgatcctg  | gaataaggat  | gatattcggt | gtgggtggcc  | taccaccata | 240 |
| actggtcaaa  | caaaagacca  | gtatggggat  | gtggtacatg | ttcccaatat  | gaaggtaatt | 300 |
| ataactggat  | taaattagca  | gacatctata  | tactggctgc | aatgactgat  | aaaattttag | 360 |
| aaatgccaa   | tgctgagrgt  | ccatttggtc  | tacctctttt | atataaagg   | tgatgctgaa | 420 |
| agtttggtta  | aatgacttgt  | ttatattaat  | tagtcccaa  | gtgtccaagt  | tacacctgtt | 480 |
| ttttttgtga  | gtttgttctt  | tacattttgc  | tacctgttac | ggggactcaa  | aggagggata | 540 |
| agaaagtatc  | catctaaaga  | gtgctagaca  | catacagtga | agccctcaa   | tatgtattga | 600 |
| ttgaataaat  | gcatgaaaga  | atacattttt  | aaattttgtg | tatagttttg  | aaagactcaa | 660 |
| gtacgttctg  | tgtttggtat  | tactgaaacc  | acatttttaa | aataacactc  | attaagttag | 720 |
| aaatatatga  | gttttagattg | taaaagaatg  | aggaattgaa | atagttgtat  | accatattga | 780 |
| tgaatataga  | gttttttagga | tacctcttac  | ctgaaatatt | aataataatg  | tttncagagc | 840 |
| atattataca  | taattatttg  | tgatttaatc  | tgtaatatg  | aatatctcat  | ttaaaacttt | 900 |
| tattttctgaa | aaaattatat  | tgaataaaat  | tttatatagg | cagtcccccag | cccttttctc | 960 |
| cttcaaagtt  | gtcttataga  | gtgattgggt  |            |             |            | 990 |

&lt;210&gt; 25

&lt;211&gt; 1208

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 25

|             |            |            |             |            |             |      |
|-------------|------------|------------|-------------|------------|-------------|------|
| taatcgctac  | tatagggaaa | gctggtcgct | gcagggtaccg | gtccggaatt | ccgggtcgac  | 60   |
| ccacgcgtcc  | gagcgaaatg | gcgcctccgg | cccccgccc   | ggcctccggc | ggctccgggg  | 120  |
| aggtagacga  | gctgttcgac | gtaaagaacg | ccttctacat  | cggcagctac | cagcagtgca  | 180  |
| taaacgaggg  | gcasgggtga | agctrtcaag | cccagagaga  | gacgtggaga | gggacgtctt  | 240  |
| cctgtataga  | gcgtacctgg | cgcagaggaa | gttcgggtgtg | gtcctggatg | agatcaagcc  | 300  |
| ctcctcggcc  | cctgagctcc | aggccgtgcg | catgtttgct  | gactacctcg | cccacgagag  | 360  |
| tcggagggac  | agcatcgtgg | ccgagctgga | ccgagagatg  | agcaggagck | tggacgtgac  | 420  |
| caacaccacc  | ttcctgctca | tggccgcctc | catctatctc  | cacgaccaga | accgggatgc  | 480  |
| cgccttgctg  | gcgctgcacc | agggggacag | cctggagtgc  | acagccatga | cagtgcagat  | 540  |
| cctgctgaag  | ctggaccgcc | tggacctcgc | ccggaaggag  | ctgaagagaa | tgcaggacct  | 600  |
| ggacgaggat  | gccaccctca | cccagctcgc | cactgcctgg  | gtcagcctgg | ccacgggtgg  | 660  |
| tgagaagctg  | caggatgcct | actacatctt | ccaggagatg  | gctgacaagt | gctcgccac   | 720  |
| cctgctgctg  | ctcaatgggc | aggcggcctg | ccacatggcc  | caggggcggc | gggaggccgc  | 780  |
| tgagggcctg  | ctgcaggagg | cgctagacaa | ggatagtggc  | taccrgaga  | cgctgggtcaa | 840  |
| cctcatcgct  | ctgtcccagc | acctkggcaa | gccccctgag  | gtgacaaacc | gatacctgtc  | 900  |
| ccagctgaag  | gatgccacac | ggtcccatcc | cttcatcaag  | gagtaccagg | ccaaggagaa  | 960  |
| cgaactttgac | aggctggtgc | tacagtacgc | tcccagcgct  | gaggctggcc | cagagctgtc  | 1020 |
| aggaccatga  | agccaggaca | gaggccagga | gccagccctg  | cagccctccc | caccgggcac  | 1080 |
| ccacctgcat  | ccctctgggg | caggagccca | ccccagcac   | ccccatctgt | taataaatat  | 1140 |
| ctcaactcca  | rggtgttcca | cctgaaaaaa | aaaaaaaaaa  | aaaaaaaaaa | aaaaaaaaaa  | 1200 |
| aaaaaaaaa   |            |            |             |            |             | 1208 |

&lt;210&gt; 26

&lt;211&gt; 1922

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1022)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 26

|            |            |            |            |            |            |    |
|------------|------------|------------|------------|------------|------------|----|
| gtgctgcgct | actgagcagc | gccatggagg | actctgaagc | actgggcttc | gaacacatgg | 60 |
|------------|------------|------------|------------|------------|------------|----|

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| gcctcgatcc  | cgggtccctt | caggctgtca  | ccgatctggg  | ctggctcgca  | cctacgctga  | 120  |
| tccaggagaa  | ggccatccca | ctggccctag  | aagggaagga  | cctcctggct  | cgggcccga   | 180  |
| cgggctccgg  | gaagacggcc | gcttatgcta  | ttccgatgct  | gcagctgttg  | ctccatagga  | 240  |
| aggcgacagg  | tccggtggta | gaacaggcag  | tgagaggcct  | tggtcttggt  | cctaccaagg  | 300  |
| agctggcacg  | gcaagcacag | tccatgattc  | agcagctggc  | tacctactgt  | gctcgggatg  | 360  |
| tccgagtggc  | caatgtctca | gctgctgaag  | actcagcttc  | tcagagagct  | gtgctgatgg  | 420  |
| agaagccaga  | tgtggtagta | gggaccccat  | ctcgcataatt | aagccacttg  | cagcaagaca  | 480  |
| gcctgaaact  | tcgtgactcc | ctggagcttt  | tggtgggtga  | cgaagctgac  | cttctttttt  | 540  |
| cctttggctt  | tgaagaagag | ctcaagagtc  | tcctctgtca  | cttgccccgg  | atttaccagg  | 600  |
| cttttctcat  | gtcagctact | tttaacgagg  | acgtacaagc  | actcaaggag  | ctgatattac  | 660  |
| ataacccggt  | tacccttaag | ttacaggagt  | cccagctgcc  | tgggccagac  | cagttacagc  | 720  |
| agtttcagggt | ggtctgtgag | actgagggaag | acaaattcct  | cctgctgtat  | gccctgctca  | 780  |
| agctgtcatt  | gattcggggc | aagtctctgc  | tctttgtcaa  | cactctagaa  | cggagttacc  | 840  |
| ggctacgcct  | gttcttggaa | cagttcagca  | tccccacctg  | tgtgctcaat  | ggagagcttc  | 900  |
| cactgcgctc  | caggtgccac | atcatctcac  | agttcaacca  | aggcttctac  | gactgtgtca  | 960  |
| tagcaactga  | tgctgaagtc | ctggggggccc | cagtcaaggg  | caagcgtcgg  | ggccgagggc  | 1020 |
| cnaaagggga  | caaggcctct | gatccggaag  | cagggtgtggc | cgggggcata  | gacttccacc  | 1080 |
| atgtgtctgc  | tgtgctcaac | tttgatcttc  | ccccaacccc  | tgaggcctac  | atccatcgag  | 1140 |
| ctggcaggac  | agcacgcgct | aacaaccacag | gcatagtctt  | aacctttgtg  | cttcccacgg  | 1200 |
| agcagttcca  | cttaggcaag | attgaggagc  | ttctcagtgg  | agagaacagg  | ggccccattc  | 1260 |
| tgctccccta  | ccagttccgg | atggaggaga  | tcgagggtct  | ccgctatcgc  | tgcagggatg  | 1320 |
| ccatgcgctc  | agtactaag  | caggccattc  | gggaggcaag  | attgaaggag  | atcaagggaag | 1380 |
| agcttctgca  | ttctgagaag | cttaagacat  | actttgaaga  | caaccctagg  | gacctccagc  | 1440 |
| tgctgcggca  | tgacctacct | ttgcaccccg  | cagtggtgaa  | gccccacctg  | ggccatgttc  | 1500 |
| ctgactacct  | ggttcctcct | gctctccgtg  | gcctggtrcg  | ccctcacaag  | aagcggaaga  | 1560 |
| agctgtcttc  | ctcttgtagg | aaggccaaga  | gagcaaagtc  | ccagaaccca  | ctgcgcagct  | 1620 |
| tcaagcacia  | aggaaagaaa | ttcagaccca  | cagccaagcc  | ctcctgaggt  | tggtgggcct  | 1680 |
| ctctggagct  | gagcacattg | tggagcacag  | gcttacaccc  | ttcgtggaca  | ggcgaggctc  | 1740 |
| tggtgcttac  | tgcacagcct | gaacagacag  | ttctggggcc  | ggcagtgtctg | ggccctttag  | 1800 |
| ctccttggca  | cttccaagct | ggcatcttgc  | cccttgacaa  | cagaataaaa  | atttttagctg | 1860 |
| ccccaaaaaa  | aaaaaaaaaa | aaaaaaactc  | gagggggggc  | ccgtacccaa  | ttcgccttat  | 1920 |
| aa          |            |             |             |             |             | 1922 |

&lt;210&gt; 27

&lt;211&gt; 1951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1892)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1930)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1934)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 27

|             |            |            |             |            |            |     |
|-------------|------------|------------|-------------|------------|------------|-----|
| tctgtccccag | agcgggctga | gccccaggcg | saggggtggcg | ggggagcctg | ggggagccgc | 60  |
| cgccacctcc  | acgggcctct | ctgagctcgg | acaccagcgc  | cctgtcctat | gactctgtca | 120 |
| agtacacgct  | ggtggtagat | gagcatgcac | agctggagct  | ggtgagcctg | cgccgtgctt | 180 |

|             |            |             |             |            |             |      |
|-------------|------------|-------------|-------------|------------|-------------|------|
| cggagactac  | agtgacgaga | gtgactctgc  | caccgtctat  | gacaactgtg | cctccgtctc  | 240  |
| ctcgccctat  | gagtcggcca | tcggagagga  | atatgaggag  | gccccgcggc | cccagccccc  | 300  |
| tgcctgcctc  | tccgaggaac | tccacgcctg  | atgaaccgga  | cgtccatttc | tccaagaaat  | 360  |
| tcttgaacgt  | yttcatgagt | ggccgctccc  | gctcctccag  | tgetgagtc  | ttcgggctgt  | 420  |
| tctcctgcat  | catcaacggg | gaggagcagg  | agcagaccca  | cggggccata | ttcagggttg  | 480  |
| tgccctcgaca | cgaagacgaa | cttgagctgg  | aagtggatga  | ccctctgcta | gtggagctcc  | 540  |
| aggctgaaga  | ctactggtac | gaggcctaca  | acatgcgcac  | tggtgcccgg | ggtgtctttc  | 600  |
| ctgcctatta  | cgccatcgag | gtcaccaagg  | agcccagagca | catggcagcc | ctggccaaaa  | 660  |
| acagtgactg  | ggtggaccag | ttccgggtga  | agttcctggg  | ctcagtcag  | gttccctatc  | 720  |
| acaagggcaa  | tgacgtcctc | tgtgctgcta  | tgcaaaagat  | tgccaccacc | cgccggtcca  | 780  |
| ccgtgcactt  | taaccgccc  | tccagctgtg  | tcctggagat  | cagcgtgcgg | ggtgtgaaga  | 840  |
| taggcgtcaa  | ggccgatgac | tcccaggagg  | ccaaggggaa  | taaatgtagc | cactttttcc  | 900  |
| agttaaaaaa  | catctctttc | tgccgatatc  | atccaaagaa  | caacaagtac | tttgggttca  | 960  |
| tcaccaagca  | ccccgccgac | caccggtttg  | cctgccacgt  | ctttgtgtct | gaagactcca  | 1020 |
| ccaaagccct  | ggcagagtc  | gtggggagag  | cattccagca  | gttctacaag | cagtttgtgg  | 1080 |
| agtacacctg  | ccccacagaa | gatattctacc | tggagtagct  | gtgcagcccc | gccctctgcg  | 1140 |
| tccccagcc   | ctcaggccag | tgccaggaca  | gctggctgct  | gacaggatgt | ggcactgctt  | 1200 |
| gaggaggggc  | acctgccacc | gccagaggac  | aaggaagtgg  | ggcgtggcc  | cagggtaggg  | 1260 |
| gagggtgggg  | caatggggag | aggcaaatgc  | agtttattgt  | aatatatggg | attagattca  | 1320 |
| tctatggagg  | gcagagtggg | ctgcctgggg  | attgggaggg  | acagggcttg | gggagcaggt  | 1380 |
| ctctggcaga  | gaaggatgtc | cgttccagga  | gcacacggcc  | ctgccccatc | ctgggcctta  | 1440 |
| cctcccctgc  | cagggtctcg | gcgctgtggc  | tcctgccttg  | atgaagcccg | tgtcctgcct  | 1500 |
| tgatgaagcc  | tgtgccacct | gcaagtgc    | gccctgcccc  | tgccccaacc | cccaccgaag  | 1560 |
| agccctgagc  | tcaggctgag | cccagccacc  | tcccaggac   | tttccagtga | ggaaatggca  | 1620 |
| acacgtggag  | gtgaagtccc | tgttctcagc  | tccgtcatct  | gcggggcttc | tggttggtctc | 1680 |
| ctgccactga  | cctcaccggc | atgctggcct  | gtggcaggcc  | taggacctca | ggcggggagg  | 1740 |
| aggagctgcc  | gcaagggcct | gtcccagcag  | aagagggagg  | cttctgact  | gacacaggcc  | 1800 |
| agccccatct  | tggtcctgtc | accctggccc  | caactattaa  | agtgccattt | cctgtcaaaa  | 1860 |
| aaaaaaaaaa  | aaaatcgggg | ggggcccggg  | anccaatttc  | ccccaaaaag | gggggttata  | 1920 |
| aaaattcccn  | ggcngtggtt | ttaaaaattc  | g           |            |             | 1951 |

&lt;210&gt; 28

&lt;211&gt; 3989

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 28

|            |            |             |            |            |             |     |
|------------|------------|-------------|------------|------------|-------------|-----|
| ggcacaggcc | gcagggnacc | tatggggcgca | tataggttgt | aatgaaactg | tagtctcagt  | 60  |
| tggaagccta | gacatgaaat | gggtcagtga  | gcaaggctct | attcctagtc | tccagccatg  | 120 |
| cctgtggaac | ctgarccrc  | tctcagcaca  | ttggaccag  | gcagatgyaa | aaaattcaca  | 180 |
| gaactatgat | ttggactcaa | gggtttgtag  | atttcctcct | tcattcta   | ttcagtgtct  | 240 |
| aaaattcctg | catcortgaa | cgagctgggc  | atttgatgag | acagggcyga | atactgcagt  | 300 |
| tttcctccta | gaaatcatct | ggggcatttt  | ctttgaactg | atgggaacaa | taaggcataa  | 360 |
| ctgtttgcac | aaacttggga | taartgattt  | tgggataacg | atctaccaga | atggggatat  | 420 |
| ttcacccttg | gttctgagat | gcaaaccaaa  | gaatatcatg | accagctttc | aggcctcctg  | 480 |
| aagtatatct | ctcacattgt | cctgttctca  | tgctgaggag | cctgagatcc | ctgtgtgggg  | 540 |
| attagacagt | ggactgttat | gggtgtaggt  | gaattggctt | attttgtctg | tcctgtctctg | 600 |
| aatgtattgc | aggaaytaaa | aaggaccaag  | aagaggaaga | agaccaaggc | ccaccatgcc  | 660 |
| ccaggctcag | cagggagctg | ctggaggtag  | tagagcctga | agtcttgag  | gactcaactg  | 720 |
| atagatgtta | ttcaactcct | tccagtgtgc  | ttgaacagcc | tgactcctgc | cagccctatg  | 780 |
| gaagttcctt | ttatgcattg | gaggaaaaac  | atgttggtt  | ttctcttgac | gtgggagaaa  | 840 |
| ttgaaaagaa | ggggaagggg | aagaaaagaa  | ggggaagaag | atcaaagaag | gaaagaagaa  | 900 |

|            |             |             |             |            |             |      |
|------------|-------------|-------------|-------------|------------|-------------|------|
| ggggaagaaa | agaaggggaa  | gaagatcaaa  | accacccatg  | ccccaggctc | agcaggggagc | 960  |
| tgctggatga | gaaagrgcct  | gaagtcttgc  | aggactcact  | ggatagatgt | tattcaactc  | 1020 |
| cttcagttgt | gttgaactgt  | gtgactcatg  | ccagccctac  | agaagtgcct | tttatgtatt  | 1080 |
| ggagcaacag | catgttggct  | tggtctgtga  | catggatgaa  | attgaaaagt | accaagaagt  | 1140 |
| ggaagaagac | caagacccat  | catgccccag  | gctcagcagg  | gagctgctgg | atgagaaaga  | 1200 |
| gcctgaagtc | ttgcaggact  | cactggatag  | atgttattcg  | actccttcag | gttatcctga  | 1260 |
| actgcctgac | ttaggccagc  | cctacagcag  | tgckgtttac  | tcattggagg | amcaktacct  | 1320 |
| tggtctkkct | cttgacgtgg  | asaaattgaa  | aagaagggga  | aggggaaraa | aagaagggga  | 1380 |
| agaagatcaa | agaaggaag   | aagaagggga  | agaaaagaag  | gggaagaaga | tcaaaacca   | 1440 |
| ccatgcccc  | ggctcagcag  | ggagctgctg  | gatgagaaag  | ggcctgaagt | cttgaggac   | 1500 |
| tcactggata | gatgttattc  | aactccttca  | ggttgtcttg  | aactgactga | ctcatgccag  | 1560 |
| ccctacagaa | gtgcctttta  | yrtattggag  | caacagygtg  | ttggcttggc | tggtgacatg  | 1620 |
| gatgaaattg | aaaagtacca  | agaagtggaa  | gaagaccaag  | acccatcatg | ccccaggctc  | 1680 |
| agcagggagc | tgctggatga  | gaaagagcct  | gaagtcttgc  | aggactcact | ggatagatgt  | 1740 |
| tattcgactc | cttcagggtta | tcttgaactg  | cctgacttag  | gccagcccta | cagcagtgct  | 1800 |
| gtttactcat | tggaggaaca  | gtaccttggc  | ttggctcttg  | acgtggacag | aattaaaaag  | 1860 |
| gaccaagaag | aggaagaaga  | ccaaggccca  | ccatgcccc   | ggctcagcag | ggagctgctg  | 1920 |
| gaggtagtag | agcctgaagt  | cttgaggac   | tcactggata  | gatgttattc | aactccttcc  | 1980 |
| agttgtcttg | aacagcctga  | ctcctgccag  | ccctatggaa  | gttcccttta | tgcattggag  | 2040 |
| gaaaaacatg | ttggcttttc  | tcttgacgtg  | ggagaaattg  | aaaagaaggg | gaaggggaag  | 2100 |
| aaaagaaggg | gaagaagatc  | aamgaagraa  | agaagaaggg  | gaagaaaaga | aggggaagaa  | 2160 |
| gatcaaaacc | caccatgccc  | caggctcaac  | ggcgtgctga  | tggaaagtga | agagcstgaa  | 2220 |
| gtcttacagg | actcactgga  | tagatgttat  | togactccgt  | caatgtactt | tgaactacct  | 2280 |
| gactcattcc | agcactacag  | aagtgtgttt  | tactcatttg  | aggaacagca | catcagcttc  | 2340 |
| gccctttacg | tggacaatag  | gttttttact  | ttgacgggtga | caagtctcca | cctggtgttc  | 2400 |
| cagatgggag | tcataattccc | acaataagca  | goccttasta  | akccgagaga | tgctattcct  | 2460 |
| gcaggcagga | cctataggca  | mgtgaagatt  | tgaatgaaag  | tacagttcca | tttgggaagcc | 2520 |
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| tgccagacat | gccgggagtg  | atcagtcrga  | cattttaatt  | tgaaccacgt | atctctgggt  | 2700 |
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| tcaaggtcak | tgctatcttt  | gtgttttagct | catccaaagg  | tgttaccctg | gtttcaatga  | 2820 |
| acctaaccct | attctttgtg  | tcttcagtg   | tggtctgttt  | tagctgatcc | atctgtaaca  | 2880 |
| caggagggat | ccttggctga  | ggattgtatt  | tcagaaccac  | caactgctct | tgacaattgt  | 2940 |
| taaccogcta | grctcctttg  | gttagagaag  | ccacagtcct  | tcagcctcca | attggtgtca  | 3000 |
| gtacttagga | agaccacagc  | tagatggaca  | aacagcattg  | ggaggcctta | gccctgctcc  | 3060 |
| tctcrattcc | atcctgtaga  | gaacaggagt  | caggagccgc  | tggcaggaga | cagcatgtca  | 3120 |
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| ctgagtttca | taggaggtaa  | tcaccagaca  | actgcagaat  | gtrgarcact | gagcaggaca  | 3240 |
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| agatattttg | ggttcaaaaa  | aagtaaaaaag | ataatgtagc  | tgcatttctt | tagttatttt  | 3360 |
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| agacacctta | cttataatga  | agtatttggg  | aggggtggtt  | tcaaaattag | aatgtcctg   | 3720 |
| tattccratg | atcatcctgt  | aaacatttta  | tcatttatta  | atcatccctg | cctgtgtcta  | 3780 |
| ttattatatt | catatctcta  | cgctggaaac  | tttctgcctc  | aatgtttact | gtgcctttgt  | 3840 |
| ttttgctagt | gtgtgttgtt  | gaaaaaaaaa  | acattctctg  | cctgagtttt | aatttttgtc  | 3900 |
| caaagttatt | ttaatctata  | caattaaaaa  | cctttgccta  | tcaaaaaaaa | aaaaaaaaaa  | 3960 |
| aaaaaaaaaa | aaaaagcgga  | cgcgtgggc   |             |            |             | 3989 |

&lt;210&gt; 29

&lt;211&gt; 3735

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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 <223> n equals a,t,g, or c

<220>  
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 <222> (3690)  
 <223> n equals a,t,g, or c

<220>  
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 <223> n equals a,t,g, or c

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 gggtgaagga actgatgtaa cagggattga agaagtagta attccaaaaa agaaaacttg 180  
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 gccttatgtg tttcaagatg atccttacct tatgccagca tcatctttgg aatctcgttc 300  
 atttttactg gcaaagaaat ccggggagaa tgtggccaag tttattatta attcataccc 360  
 caaatatttt cagaaggaca tagctgaacc tcatataccg tgtttaatgc ctgagtactt 420  
 tgaacctcag atcaaagaca taagtgaagc cgccctgaag gaacgaattg agctcagaaa 480  
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 tgattaccat tttcaacaaa ctggacagtc agaagcattg gaagaggaaa atgatgagac 660  
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 gagaatcttt tctctaattg cagagaaaaa tgaacattcc tattgcacaa tgatccgagg 780  
 aatggtgaag caccgagctt atgagcaggc attaaacttg tacactgagt tactaaacaa 840  
 cagactccat gctgatgtat acacatttaa tgcattgatt gaagcaacag tatgtgcgat 900  
 aaatgagaaa tttgaggaaa aatggagtaa aatactggag ctgctaagac acatggttgc 960  
 acagaagggt aaaccaaata ttcagacttt taataccatt ctgaaatgtc tccgaagatt 1020  
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|             |            |             |            |            |            |      |
|-------------|------------|-------------|------------|------------|------------|------|
| catcttaggt  | gttcatgcag | ttctaacaca  | gttgggggtt | ggtcaatagt | ttcccaattt | 2520 |
| caggatattt  | cgatgtcaga | aataacgcat  | cttaggaatg | actaaacaag | ataatggcag | 2580 |
| tttaggctgc  | acaactggta | aaatgactgt  | agataaatgt | tgtaattagt | gtacacgttt | 2640 |
| gtatttttgt  | taatatagcc | gctgccatag  | ttttctaact | tgaacagcca | tgaatgttct | 2700 |
| atgtctccct  | tttttttttg | tctatagctg  | ttacctat   | tagtggttga | aatgagagct | 2760 |
| agtgatgaca  | gaaggatgtg | gaatgtcttc  | ttgacatcat | tgtgtattgc | tggtaatcaa | 2820 |
| gttggttaacg | actacttcta | gcagctctta  | ccactatgac | ttaagtggtc | ctggaaggca | 2880 |
| gtaagtggag  | gtttgcagca | ttcctgcctt  | catgagggtc | tctaccactg | accactttgc | 2940 |
| acgtacctgg  | ctcccagatt | tacttaggta  | ccccacgagt | cgtccacata | agcagcttca | 3000 |
| tctttacctt  | gccagagtgt | acaattatgg  | gatactctag | tctacttata | cttgtgttcc | 3060 |
| catctgtctg  | ccatcctctg | aaggccagga  | ccagctcata | catccttaga | aaccaaagta | 3120 |
| tgggttttgt  | tttctcttgg | aatgtcaggt  | cttaaggcat | ttaattgagg | gacaaaaaaa | 3180 |
| aaaaaaagcc  | gatatagtag | ctagctactt  | aagcatccat | gggtattgct | ccatatcaaa | 3240 |
| gcagatttgc  | aggacagaaa | gagtaaatta  | gccttcagtc | ttggtttaca | gcttccaagg | 3300 |
| agagccttgg  | ccacctgaaa | tgtaactcgt  | gtcccttcct | gtctctagtt | catcagcacc | 3360 |
| tgcagatgcc  | tgactcttgt | tagccttact  | attcaatata | gtccttagat | tcacggtatg | 3420 |
| ctcttctcta  | tccaggcacc | tattctgaat  | caccatgttg | ctctgcagct | agagttgata | 3480 |
| ggagaaaaatc | caattgggta | taggtgctat  | gaattttag  | tagactttca | aaatgagtga | 3540 |
| ttgttagct   | tggtactttt | aagtttggg   | tacagatcct | ccaaacccat | actctgagca | 3600 |
| attaactgcc  | ttgaacatag | agaaaattaa  | ggcctcacag | gatgagtctc | cattctctgt | 3660 |
| aaatgcttat  | tttatcatag | tcttttagccn | ctactatgag | taaaatgttc | tcttcngccg | 3720 |
| ggtgtggtga  | ctcac      |             |            |            |            | 3735 |

&lt;210&gt; 30

&lt;211&gt; 1667

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1628)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 30

|             |             |             |            |            |            |      |
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| agacttaaag  | ttagagctgc  | gacgactacg  | agataaacat | ctcaaagaga | ttcaggacct | 120  |
| gcagagtcgc  | cagaagcatg  | aaattgaatc  | tttgtatacc | aaactgggca | aggtgcccc  | 180  |
| tgtgttatt   | attccccag   | ctgctccctt  | ttcagggaga | agacgacgac | ccactaaaag | 240  |
| caaaggcagc  | aaatctagtc  | gaagcagttc  | cttgggggat | aaaagccccc | agctttcagg | 300  |
| taacctgtct  | ggtcagagtg  | cagcttcagt  | cttgaccccc | cagcagaccc | tccaccttcc | 360  |
| tggcaacatc  | ccagagtcgg  | ggcagaatca  | gctgttacag | ccccttaagc | catctccctc | 420  |
| cagtgaacaac | ctctattcag  | ccttcaccag  | tgatggtgcc | atttcagtac | caagcctttc | 480  |
| tgctccaggt  | caaggaaacca | gcagcacaaa  | cactgttggg | gcaacagtga | acagccaagc | 540  |
| cgcccaagct  | cagcctcctg  | ccatgacgtc  | cagcaggaag | ggcacattca | cagatgactt | 600  |
| gcacaagttg  | gtagacaatt  | gggcccagaga | tgccatgaat | ctctcaggca | ggagaggaag | 660  |
| caaagggcac  | atgaattatg  | agggccctgg  | aatggcaagg | aagttctctg | cacctgggca | 720  |
| actgtgcatac | tccatgacct  | cgaacctggg  | tggctctgcc | cccatctctg | cagcatcagc | 780  |
| tacctctcta  | ggtcacttca  | ccaagtctat  | gtgcccccca | cagcagtatg | gctttccagc | 840  |
| taccccat    | ggcgctcaat  | ggagtgggac  | gggtggccca | gcaccacagc | cacttggcca | 900  |
| gttccaacct  | gtgggaactg  | cctccttgca  | gaatttcaac | atcagcaatt | tgcagaaatc | 960  |
| catcagcaac  | cccccaggct  | ccaacctgcg  | gaccacttag | acctagagac | attaactgaa | 1020 |
| tagatctggg  | ggcaggagat  | ggaatgctga  | gggggtgggt | gggggtggga | agtagcctat | 1080 |
| atactaacta  | ctagtgtctg  | atttaactgg  | ttatttcttg | ccagagggga | atgtttttaa | 1140 |
| tactgcattg  | agccctcaga  | atggagagtc  | tcccccgctc | cagttatttg | aatgggagag | 1200 |
| gaaggaaaaga | acagcttttt  | tgtcaagggg  | ccatgcttct | ataaggaagc | tggagaaatc | 1260 |
| atactcagta  | atgaggatga  | gggctaggaa  | agtcttgttc | ataaggaagc | tggagaaatc | 1320 |
| aatgtaaaat  | caaaccatc   | tgtaatttgc  | agtgggtgga | gctcttgctt | ttggtacatg | 1380 |

|            |             |            |            |            |            |      |
|------------|-------------|------------|------------|------------|------------|------|
| ccctgaatcc | ctcactccct  | caagaatccg | aaccacagga | caaaaaccac | ctactgggct | 1440 |
| ctctcctacc | ctgcccctct  | cccttttttt | taccctctct | ttttttattt | tttctttgct | 1500 |
| ctttagaacc | cagtgaaaaa  | taccagggtg | ctgggggtgc | actctttctt | atgataggtc | 1560 |
| attagtgcct | taagcaaaaag | atattagcag | ctttgactgc | agcattagca | attaggraaa | 1620 |
| aaaaaaanwa | aaaactcgag  | ggggggcccc | gttacccaat | tcgccct    |            | 1667 |

<210> 31  
 <211> 1408  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1385)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (1395)  
 <223> n equals a,t,g, or c

|             |            |            |            |             |            |      |
|-------------|------------|------------|------------|-------------|------------|------|
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| tagatgggtca | gctttctgta | gcagtgagaa | ccctacattt | caaattgtgga | tagcaccttt | 120  |
| gcggggaaac  | atcacttggc | acatctgcat | tcttttttga | cacagggctc  | cactctgttg | 180  |
| cccaggctag  | agtgcattgg | acgatcttag | ctcactgcaa | cctccacctc  | ccaagttcaa | 240  |
| gcgattcttc  | tgcctcagcc | tcctgagcag | ctgggatcac | agacatgcgc  | taccatgccc | 300  |
| agctaatttt  | ttgtattttt | tgtktgtttg | tttttgtttk | taagtagaga  | cgggctttca | 360  |
| ccacgttggs  | caggcaggtc | tcgaactcct | gamctcaggt | gatccacca   | catctgcgtt | 420  |
| ccaatatctt  | tctcaacata | atgatagccg | taattaatat | tttccagtac  | atttttatgc | 480  |
| ctttacacac  | gagagtggta | gacagacaca | aaccagatc  | tgtctgactc  | caaagcccgt | 540  |
| ttgtcatcat  | tccttttacg | gtatcctata | gtggatcctt | ttacagaaag  | acagctttta | 600  |
| cccaacaaag  | acttaacttc | ccaggatgcc | agaaggacaa | agcgggattg  | cttttaagra | 660  |
| graaagtatc  | aagamcttat | tttataaatg | agattagata | gggaaaggca  | atztatcttt | 720  |
| attaaaaact  | gaaaaggcca | gcatagggaa | ggaggctcct | cgggtggtct  | tttcagggaa | 780  |
| atacttcagt  | tgcttttatt | agaaacagat | agtaacctaa | gttttgaggt  | aggwacagct | 840  |
| taaggcatgc  | taatgkcat  | gggtccctcc | atagtcattt | tkgtattttg  | gttwacattt | 900  |
| gagcaatagg  | cagcccttca | ctgctgctgg | aytcattcct | gccaytatta  | caggtgacag | 960  |
| aggagacagg  | aggtatgtct | tttctatatt | tawacatgct | ttatatatta  | cacaagctct | 1020 |
| tgggtatctt  | agataaacag | aagttgccta | gcactccttt | tagtgcattg  | aaccctttaa | 1080 |
| catttaagca  | aaataataaa | cagtcttttg | aggttcctta | acaatgaaac  | gtgttcgagt | 1140 |
| ggcagcagcg  | gaatccatgc | ytcttctcct | ggagtgtgca | akagtccgtg  | gtcctgagta | 1200 |
| tctcacacag  | atgtggcatt | ttatgtgtga | tgctctaatt | aaggccattg  | gtacagaacc | 1260 |
| agattcagac  | gtcctctcag | aaataatgca | ttcttttgca | aaggtgaata  | tttttctctt | 1320 |
| aaaaaatatg  | tataagggtg | tatgttcatt | tattagtctt | gctaaaaaaa  | aaaaaaaaaa | 1380 |
| acttngaggg  | ggggnccggt | acccaatt   |            |             |            | 1408 |

<210> 32  
 <211> 3186  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (24)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (666)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (682)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (3181)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (3184)  
 <223> n equals a,t,g, or c

<400> 32

|            |            |            |             |            |             |      |
|------------|------------|------------|-------------|------------|-------------|------|
| gggaggtcga | gaagccaata | agtngttttt | cattgaatcc  | tgcattgcac | tctttgtttc  | 60   |
| cttcatcatc | aatgtctttg | ttgtctcagt | stttgctgaa  | gyrttttttg | ggraaaccaa  | 120  |
| cgagcaggtg | gttgaagtct | gtacaaatac | cagcagtcct  | catgctggcc | tctttcctaa  | 180  |
| agataactcg | acactggctg | tggacatcta | caaagggggt  | gttgtgctgg | gatgttactt  | 240  |
| tgggcctgct | gcactctaca | tttgggcagt | ggggatcctg  | gctgcaggac | agagctccac  | 300  |
| catgacagga | acctattctg | gccagtttgt | catggaggga  | ttcctgaacc | taaagtggtc  | 360  |
| acgctttgcc | cgagtgggtc | tgactcgctc | tattgccatc  | atccccactc | tgcttggtgc  | 420  |
| tgtcttccaa | gatgtagagc | atctaacagg | gatgaatgac  | tttytgaatg | ttctacagag  | 480  |
| cttacagctt | ccctttgctc | tcatacccat | cctcacattt  | acgagcttgc | ggccagtaat  | 540  |
| gagtgaactt | gccaatggac | taggctggcg | gattgcagga  | ggaatctggt | cctatcatct  | 600  |
| gttccatcat | atgtactttg | tagtggwttt | tgtccgggtt  | ytaaggcatg | tgscattata  | 660  |
| tgtggnggct | gctgtggtca | ancgtggctt | atctgggctt  | tgtgttctac | ttggrttggc  | 720  |
| aatgtttgat | tgcactgggc | atgtccttcc | tggactgtgg  | gcatacggta | agcatctcta  | 780  |
| aaggcctgct | gacagaagaa | gccacccgtg | gctacgttaa  | ataacactgg | attagtctgt  | 840  |
| cttctgcagg | tagccatcag | agccagtgtg | tttctatggt  | ttactgtgtg | aacatagcca  | 900  |
| aaagtatgtg | ccgttgacaa | gactgtgttt | atgactcaac  | cgttggttgg | aaaagacttt  | 960  |
| gtttcatgtg | tatttgaag  | atggaattat | tttttccttc  | ctgacctaac | cttagaactg  | 1020 |
| gattagggtg | ggatccttga | aaagctgaca | tttgctgcta  | tcattccaac | actaaattct  | 1080 |
| taagtagttg | cccaagggcc | agctcagttt | atccttcgga  | gagacaagga | tatgcatgat  | 1140 |
| tcttaaccag | gctatatgtt | aaaaaaaaat | tggaaaatgc  | aatacatttt | ttattataca  | 1200 |
| aactacagaa | tgagtatgca | agttttattt | atcaaaatgt  | aatggatttt | taaaggctga  | 1260 |
| gaaattttcc | ttatacctac | cttttcagtt | attttaatta  | taccaaatta | tcaactagaa  | 1320 |
| tagcttcac  | catatgaaat | ataaaatgaa | gagacaccta  | gctctatcag | gcttaggatt  | 1380 |
| ctttgaactt | atttccactt | taatttctca | gtggaagtta  | agagggtgga | gaaaacaaag  | 1440 |
| aaggggaaaa | actgacaact | aacaaaacca | gcaccacatc  | gctaggtggt | gcttactaat  | 1500 |
| taccttctca | ggattttcct | cagattgaaa | agcttatgag  | gatttcttgg | gagtcctaat  | 1560 |
| aacctgcctg | ttagtacaga | gctttcctga | tgatatttac  | tcttgagcac | atgtggttgt  | 1620 |
| aaaaccttaa | ctttctttct | ccaggagggt | ggtagatagaa | acagatggta | gtattttatga | 1680 |
| actgatgttc | tcgtgaaatg | ttgagggtgg | ggagaaaaga  | ctttaaggga | ggagagccat  | 1740 |
| ctattttgtt | cctaaagcca | cctctcagca | gaatcgtcat  | gtttttctga | tgaccgctc   | 1800 |
| tgcttcatgc | ccaagatgac | ttgcgaggca | atctcaggag  | ctgtggactt | aaccattgca  | 1860 |
| aagcacactg | tctttctcag | cgttctctgc | aagtcagtag  | gtgttagtat | ggttgcaaag  | 1920 |
| ttcactgtct | cagcaaaagt | gaactgggct | acctctctac  | agctgtttcc | tcagagggaa  | 1980 |
| aaatcttgag | accagatggg | ggagctctgg | agtcagagga  | aatgggtgtc | ttcagcacia  | 2040 |
| agctgctgct | tttacttcag | ccacttctga | cattttttaca | taccgagcct | gagattgtgt  | 2100 |
| gattatctca | aatcaaatca | ctttgatgga | gataaataat  | caaaactgtt | ttatagtcac  | 2160 |



|             |            |            |            |            |             |      |
|-------------|------------|------------|------------|------------|-------------|------|
| tgatttgggtg | agaacagtaa | tggaaaatgg | tgttgaagga | cttctcattt | ttggagcttt  | 2220 |
| ccttccagag  | tcctggctga | ttgggtgtcg | ctgttcacat | gagcccccaa | aagcattatt  | 2280 |
| actgatactt  | gcacacagtc | aaaagcgcag | actggatgga | tggtctttta | taaggcattt  | 2340 |
| aagggtacac  | tactgtgttt | cactgaccat | acatttttct | tagccctca  | agtaatatag  | 2400 |
| cacagagtta  | tgaatgacaa | ttcccctaac | cattcctctt | catatctgcc | tcttcccctt  | 2460 |
| accatcgtaa  | ttctccaaac | tggtcataaa | ggcactctgt | gaagatattg | gggactgaca  | 2520 |
| tcttaagctc  | tcacctggct | gcagtaggaa | aggccaaact | gacgacaaaa | aaaaaattct  | 2580 |
| ttataaagat  | gatatggtaa | catgtatctt | tgccctgggt | ctgggtgggt | ccagtcagtc  | 2640 |
| tcagattttac | aagcatttag | gagcctaggt | aaaagctgct | agtattcttt | taaaagttac  | 2700 |
| atztatgact  | tgcaatgata | gaaaactcct | tccaattaaa | tggcatttta | taatattatg  | 2760 |
| tgtgtacttc  | acagtgttaa | aaataccctc | atacgttatt | gcatttgatc | ttcacagaaa  | 2820 |
| gtgcatttta  | accagtactc | tgggtgcaat | aaataatatg | tagaaattta | agtcctocaa  | 2880 |
| ttccagcata  | tccagtgagt | tttgacagtg | tgtttatgtg | gaatgtttaa | ggatatacaa  | 2940 |
| ttgtacttta  | tataaattgg | ttcttgttct | tcttaaatgt | gacatgaaat | aattgtgctg  | 3000 |
| ctacattata  | ctggaaatta | acaggggaaa | agggaagagc | tcttggctcc | cttgaggttc  | 3060 |
| tgctagtggg  | gttaggagtg | gttacaactg | agcttttagt | aaccatttaa | ccgtatgtaa  | 3120 |
| acttgggttc  | taattaaaaa | aaaatttctt | tttccaaaaa | aaaaaaaaaa | aaaaaaaaatt | 3180 |
| nctngg      |            |            |            |            |             | 3186 |

&lt;210&gt; 33

&lt;211&gt; 971

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (957)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (964)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 33

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| cgcgtcggaa | ctcggccgcg | ggacatccac | ggggcgcgag | tgacacgcgg | gagggagagc | 60  |
| agtgttctgc | tggagccgat | gccccaaacc | atgcatttct | tattcagatt | cattgttttc | 120 |
| ttttatctgt | ggggcctttt | tactgctcag | agacaaaaga | aagaggagag | caccgaagaa | 180 |
| gtgaaaatag | aagttttgca | tcgtccagaa | aactgctcta | agacaagcaa | gaaggagagc | 240 |
| ctactaaatg | cccattatga | cggctacctg | gctaaagacg | gctcgaaatt | ctactgcagc | 300 |
| cggacacaaa | atgaaggcca | ccccaaatgg | tttgttcttg | gtgttgggca | agtcataaaa | 360 |
| ggcctagaca | ttgctatgac | agatatgtgc | cctggagaaa | agcgaagagt | agttataccc | 420 |
| ccttcatttg | catacgga   | ggaaggctat | gcagaaggca | agattccacc | ggatgctaca | 480 |
| ttgatttttg | agattgaact | ttatgctgtg | accaaaggac | cacggagcat | tgagacattt | 540 |
| aaacaaatag | acatggacaa | tgacaggcag | ctctctaaag | ccgagataaa | cctctacttg | 600 |
| caaaggggat | ttgaaaaaga | tgagaagcca | cgtgacaagt | catatcagga | tgagttttta | 660 |
| gaagatattt | ttaagaagaa | tgaccatgat | ggtgatggct | tcatttctcc | caaggaatac | 720 |
| aatgtatacc | aacacgatga | actatagcat | atgtgtatgt | ctactttttt | tttttagcta | 780 |
| tttactgtac | tttatgtata | aaacaaagtc | acttttctcc | aagttgtatt | tgctattttt | 840 |
| cccctatgag | aagatatttt | gatctoccca | atacattgat | tttggataaa | ttaatgtgag | 900 |
| gctgttttgc | aaacttaaaa | aaaaawwaaa | aaaactsgag | gggggcccgt | acccaantcg | 960 |
| ccgnatatga | t          |            |            |            |            | 971 |

&lt;210&gt; 34

&lt;211&gt; 1792

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1767)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1768)

<223> n equals a,t,g, or c

<400> 34

|             |             |            |             |             |            |      |
|-------------|-------------|------------|-------------|-------------|------------|------|
| gaacccccctt | tctcctggta  | aagggtaagg | gggggggataa | tgtttaccac  | aggtacgaaa | 60   |
| tagtcactttt | aacattgaga  | cctctgcctc | attgaattca  | ggtttttttaa | gtacttgaaa | 120  |
| ctcttcagat  | tctccttatt  | ttagtttctt | tttacattta  | tgaagtagaa  | agcattgttt | 180  |
| tgtaaactgt  | tttggaaaata | aatagcctag | tctcttatcc  | tcttttagcgt | ggattaaagg | 240  |
| tgaagttctg  | caaattgggag | agtgttcaca | gtagatagct  | cagattgatt  | gaacacattt | 300  |
| gaggaagaga  | ctcctgcatg  | agataccagc | atthtttacia | atacttttta  | tgtacattct | 360  |
| ttatthttgtc | atthttgtcaa | ccctctcccc | aagcacatct  | tctttccttt  | tactatgtct | 420  |
| atgtagggaa  | aaacaaaaca  | aaaaattgca | cttacgttac  | actcccaaaa  | tgtgggtaat | 480  |
| ccgtgtcttt  | caaaaaacat  | ttctgttttt | tgthttgttt  | tggtcagtcc  | attgcataag | 540  |
| tgacaagttt  | gggtgcttgt  | ggcacgtatg | tatgaagcgg  | gagggggatg  | asaattgcct | 600  |
| gtccttcagt  | argctgtaaa  | agtaatttac | atgtaagtaa  | aaagggaaaa  | tagaatagat | 660  |
| gccaaagtca  | tttattcagt  | ccttagtttt | cttatgtggc  | attactgcat  | ctgctagtta | 720  |
| gtgagaaagc  | accctcagct  | tttactgctc | ccctccctgc  | ctgccaacac  | acttgatgtg | 780  |
| tgcaaacagc  | cctcaagtat  | ctgtcagatg | acctatataa  | ggatttgaat  | aaggtattct | 840  |
| tgtcagttta  | gaaatggact  | ggataaaact | tacttggttg  | tcattatttt  | atctcatttg | 900  |
| tcctgtttaca | tgccctatgt  | taagataatt | atattgccac  | taataatcaa  | gatgctaaat | 960  |
| gagtattaca  | actggctaat  | atcatttttt | atatacaagg  | gtatgtgtat  | atthtgaatt | 1020 |
| grtatgagaa  | actcattttg  | acccatttga | gtgatattgc  | acaacaaaca  | cagataycta | 1080 |
| cagactccgt  | tttcattttc  | tcgtgttctt | tatgataatg  | atctttgtag  | attggttatt | 1140 |
| tctgtacttt  | atctgtaata  | aactttgtag | atcctgtgaa  | ccattacttt  | gcctaaatca | 1200 |
| cttgagactt  | gagtctttta  | taacaaagca | tcaatattca  | ctaaagtcaa  | tctcttttga | 1260 |
| gtttctgtga  | cttggtctaga | agctcttgac | actaaaggat  | tagtgttaat  | tttccctggg | 1320 |
| gggtgtccac  | tagggcatta  | ctgtataatg | acttgatgtt  | gccacataga  | cttcaagata | 1380 |
| tataatattt  | tgaggatttt  | gttgattggc | ctatgtttta  | ttgcatagtg  | tgaaacgtgt | 1440 |
| aaagcttggt  | taacctgtat  | atagatagct | tattgttgac  | tagttatagt  | gtatttaggg | 1500 |
| ttgcctgtaa  | tatttaagct  | tctttactga | tgtgtgtgct  | ggtaggaaca  | tataattttt | 1560 |
| gtacattata  | tttactgaga  | tgthgccttt | tttattttac  | aaatactttg  | gaattccaat | 1620 |
| gtgttttttg  | cttccgtgag  | gattaatttg | gaaaggthtt  | taatgacatt  | ccactgattt | 1680 |
| cagattttgc  | ttgagattga  | cttcaataaa | ttgtcctgta  | tgthccaaaa  | aaaaattaaa | 1740 |
| aaactcgagg  | ggggcccggt  | acccaanncg | cgggatatga  | tcgtaaacaa  | tc         | 1792 |

<210> 35

<211> 896

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (870)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (877)

<223> n equals a,t,g, or c

<400> 35

|             |             |            |            |            |            |     |
|-------------|-------------|------------|------------|------------|------------|-----|
| agttgnanac  | aacaggacct  | gagtccttgg | gcagcaccag | taggttgccc | cytgcytcyt | 60  |
| gccagcytca  | cytgccacyt  | tytgccccty | tcgggatgcc | ttcgagaca  | gagytyttcg | 120 |
| ctgcctgtgg  | tggccaytct  | ttgcttttgg | ttytcttgcc | ccttggcctc | cctttttgtc | 180 |
| cccgggcagc  | cttggtgtgac | ctgccctttt | ccctcccttc | ctttccagga | caagcacgcc | 240 |
| gaggaggtgc  | ggaaaaacaa  | ggagctgaag | gaagaggcct | ccaggtaaag | cctagaggcc | 300 |
| aaagaacttt  | ccaggtcagc  | cggacagctc | cagcagctcc | acgttccagg | cagcctcgmc | 360 |
| cgccggctgc  | gctcccagca  | ctgggggttg | gggggagggg | ggtggccaag | gggcgtttcc | 420 |
| tctgcttttg  | gtgtttgtac  | atgttaagaa | ttgaccagtg | aagccatcct | atttgtttcc | 480 |
| ggggaacaat  | gacgggggtg  | garaggggag | aggagagagt | ttgggaaagg | gagatggaga | 540 |
| agaactcaag  | gacattgcaa  | ccctgcccgg | cgcagatctg | attttcacat | ctctacctgg | 600 |
| acattgagcc  | tcccaggcac  | catgttgagg | agagatgaaa | accagggcgg | tagaacttca | 660 |
| gggtgaagga  | cagagtcctg  | ggtggggcag | cggctgcagg | gcgcaccaga | gaacccagcc | 720 |
| agaggggggtg | tgagtaccag  | tggtgttgct | tccaccctgc | agcaggtggg | atgaggtctg | 780 |
| tgtgtgtgtg  | tgaacatca   | ttttttgatc | atcatgacca | atgaaacatt | gaaaaaaaaa | 840 |
| aaaaaaactg  | gagggggggc  | cgtacccaan | tcgccgnata | gtgatcgtaa | acaatc     | 896 |

<210> 36

<211> 912

<212> DNA

<213> Homo sapiens

<400> 36

|             |             |            |             |            |            |     |
|-------------|-------------|------------|-------------|------------|------------|-----|
| tcgacccacg  | cgtccgggtca | gccagtcgca | tccagccatg  | acagccttct | gctccctgct | 60  |
| cctgcaagcg  | cagagcctcc  | taccaggac  | catggcagcc  | ccccaggaca | gcctcagacc | 120 |
| aggggaggaa  | gacgaaggga  | tgcagctgct | acagacaaag  | gactccatgg | ccaagggagc | 180 |
| taggcccggg  | gccakccgcg  | gcagggctcg | ctgggggtctg | gcctacacgc | tgctgcacaa | 240 |
| cccaaccctg  | caggtcttcc  | gcaagacggc | cctgttgggt  | gccaatggtg | cccagccctg | 300 |
| arggcaggga  | akgtcaaccc  | acctgcccct | ctgtgctgag  | gcatgttctt | gcctaccatc | 360 |
| ctcctccctc  | cccggctctc  | ctcccagcat | cacaccagcc  | atgcagccag | caggtcctcc | 420 |
| ggatcacagt  | ggttkgggtg  | aggtctgtct | gcactgggag  | cctcargarg | gctctgctcc | 480 |
| acccacttgg  | ctatgggaga  | gccagcaggg | gttctggaga  | aaaaaactgg | tgggttaggg | 540 |
| ccttgggtcca | ggagccagtt  | gagccagggc | agccacatcc  | aggcgtctcc | ctaccctggc | 600 |
| tctgccatca  | gccttgaagg  | gcctcgatga | agccttctct  | ggaaccactc | cagcccagct | 660 |
| ccacctcagc  | cttggccttc  | acgctgtgga | agcagccaag  | gcacttcctc | accccytcag | 720 |
| cgccacggac  | ctytytgggg  | agtggccgga | aagctcccs   | gcctytggcc | tgaggggcag | 780 |
| cccaagtcac  | gactcagacc  | aggtcccaca | ctgagctgcc  | cacactcgag | agccagatat | 840 |
| ttttgtagtt  | ttttatkcctt | tggctattat | gaaagaggtt  | agtgtgttcc | ctgcaataaa | 900 |
| cttgttctctg | ag          |            |             |            |            | 912 |

<210> 37

<211> 1382

<212> DNA

<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (787)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 37

|            |             |            |             |            |             |      |
|------------|-------------|------------|-------------|------------|-------------|------|
| aattcggcac | gagcggagggc | gagggaaact | ragggcgaaa  | gttggtgtgc | gtgttggcag  | 60   |
| gagggcctag | aagggaaaaga | ctgtctagt  | ggacaatgtc  | atattataaa | tttgggaatgc | 120  |
| tgaatagaaa | attatagatt  | ttgatattga | aggaaatgaa  | gcgaagcyta | aatgaaaatt  | 180  |
| cagctcgaag | tacagcaggc  | tgtttgcctg | ttcogttggt  | caatcagaaa | aagaggaaca  | 240  |
| gacagccatt | aacttcta    | ccacttaaag | atgattcagg  | tatcagtacc | ccttctgaca  | 300  |
| attatgattt | tcctcctcta  | cctacagatt | gggcctggga  | agctgtgaat | ccagagttkg  | 360  |
| ctcctgtaat | gaaaacagtg  | gacaccgggc | aaataccaca  | ttcagtttct | cgtcctctga  | 420  |
| gaagtcaaga | ttctgtcttt  | aactctattc | aatcaaatac  | tggagaagc  | caggggtggtt | 480  |
| ggagctacag | agatggtaac  | aaaaatacca | gcttgaaaaac | ttggrataaa | aatgatttta  | 540  |
| agcctcaatg | taaacgaaca  | aacttagtgg | caaatagatg  | aaaaaattct | tgtccaatga  | 600  |
| gttcgggaag | tcaacaacaa  | aaacaattaa | gaacacctga  | acctcctaac | ttatctcgca  | 660  |
| acaaagaaac | cgagctactc  | agacaaacac | attcatcaaa  | aatatctggc | tgcacaatga  | 720  |
| gagggctaga | caaaaacagt  | gcactacaga | cacttaagcc  | caattttcaa | caaaatcaat  | 780  |
| ataaganaca | aatgttggat  | gatattccag | aagacaacac  | cctgaaggaa | acctcattgt  | 840  |
| atcagttaca | gtttaaggaa  | aaagctagtt | ctttaagaat  | tatttctgca | gttattgaaa  | 900  |
| gcatgaagta | ttggcgtgaa  | catgcacaga | aaactgtact  | tctttttgaa | gtattagctg  | 960  |
| ttcttgattc | agctgttaca  | cctggcccat | attattcgaa  | gacttttctt | atgagggatg  | 1020 |
| ggaaaaatac | tctgccttgt  | gtcttttatg | aaatcgatcg  | tgaacttccg | agactgatta  | 1080 |
| gagggcaggt | tcatagatgt  | gttggcaact | atgaccagaa  | aaagaacatt | ttccaatgtg  | 1140 |
| tttctgtcag | accggcgtct  | gtttctgagc | aaaaaacttt  | ccaggcattt | gtcaaaattg  | 1200 |
| cagatgttga | gatgcagtat  | tatattaatg | tgatgaatga  | aacttaagta | gtgataaaaag | 1260 |
| gaagtttagc | ataaattata  | gcagttttct | gttattgctt  | aatttaccat | ctccatagtt  | 1320 |
| ttatagctac | tattgtattt  | cacttggtga | attaaagtat  | ttgaattctt | ttaaaaaaaa  | 1380 |
| aa         |             |            |             |            |             | 1382 |

&lt;210&gt; 38

&lt;211&gt; 872

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gggctacttc | aaagccctgg | gccttatttc | ttcaggtaaa | aaaatataaa | gtcagatctc | 60  |
| atcccggctg | gccatgctgt | tagacccttt | catccttctc | ttctgcctct | tctcaacagc | 120 |
| tgcccagtc  | tgtttggaa  | tcataacat  | acagttctaa | tactgatgta | tttaccctca | 180 |
| taagccactc | aaccagaat  | cttatttgaa | ttataatcca | gaaacatcag | gtgacgtgtg | 240 |
| agactactgt | atgagaaaga | gacagtttaa | gggtcagtc  | aatggaaaaa | agagttctca | 300 |
| gagctttctt | tagcttattc | tcatacaaga | gctttctctg | cagaaggaa  | ctactggttc | 360 |
| ctcctttcca | gtcctagaaa | tcctgacct  | gagtggttta | atcctgctag | cacctctctc | 420 |
| tcgactctg  | gtgccaatg  | actccaggaa | ctgggccatg | atgtggtggg | aatgacctta | 480 |
| ccctgagcat | gtcactcatg | cattgaacaa | cagctaagag | cagagcttag | agcttagagc | 540 |
| tgggccctgt | aaggtgagag | gaatcacatc | ctgcagaagt | ctgtcctgag | aagcaggtac | 600 |
| tcctgtcaca | gcagagacac | agtggatacc | tgagtaacaa | taatacaaga | caggacgtgg | 660 |
| gmacagcaaa | agatttgggt | gtcagaagar | gccgagaaca | cttycaggca | ggaacattca | 720 |
| rarttgttct | tggaggaart | aggcmcsaag | gctgggcagg | atttcmcggg | gcagagatgg | 780 |
| agcaagcaat | tgaatgaaa  | gccatggcat | gggaaaagga | gcactggcca | cagggagtg  | 840 |
| aacgttgtga | tgcaaggcca | ctgtggagcc | at         |            |            | 872 |

&lt;210&gt; 39

&lt;211&gt; 812

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (794)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (806)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (810)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 39

|             |            |             |             |            |            |     |
|-------------|------------|-------------|-------------|------------|------------|-----|
| ggcagaggct  | caccccagca | gagattgagg  | gggaaccgtg  | atgaaatttt | taagtattct | 60  |
| gcttgatgat  | aataatttty | ctcttatgtt  | aatgttggct  | ccgtttgggt | gtttagcttt | 120 |
| tgaaggaggt  | atgaaaatgc | ggaatggggc  | tttggggcct  | gaggagggtg | gatctctagt | 180 |
| gtttaaaaaa  | tttaattgca | caaataagaaa | taattcaccc  | acattattga | accccactaa | 240 |
| agcatatcct  | ttttgtccat | attcctttcc  | tgtgtccctc  | gtgtgtacca | ttattactca | 300 |
| gttgtgattt  | gagctcgttc | cacttaaagt  | cattcataga  | tacttttgcg | tcgtgttkga | 360 |
| atattttattg | aatttctatt | ctgtgtttta  | cttaattact  | ttattatgga | acctttacac | 420 |
| aggctcgggtg | tacttgttct | ttgaaaagtc  | ttatgttgac  | caccatcact | gagcatatag | 480 |
| ctttttcctt  | atttccttgg | gataattacc  | cgaagtggaa  | ataccgaatc | aaacttctgt | 540 |
| tttctttctt  | tggcactatt | atataaattg  | ttttccaaac  | aaggcatgtt | tacaatagac | 600 |
| atttttcaaa  | atctgggtat | ttgtcctatt  | ttgtctctctg | tatgcagaat | tcagcggggt | 660 |
| gccaaagtctg | tttctgtgtg | ggttgagaga  | caggctgtgc  | agccactgtg | tgcataggac | 720 |
| taactactac  | aatcatgct  | gagaccgagc  | tatttttgct  | gcttagargc | tttgcagcct | 780 |
| tgagtaagtt  | tcgncatctg | gaaacnttgn  | aa          |            |            | 812 |

&lt;210&gt; 40

&lt;211&gt; 1515

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 40

|             |            |             |            |            |            |     |
|-------------|------------|-------------|------------|------------|------------|-----|
| aattcggcac  | gagggaaatt | caagcacttt  | tcctaaaaga | agggggaatg | gatgctgaaa | 60  |
| caacacgtnt  | cccacaaagg | gagcagacac  | tgggcttgtg | aagctgcccc | ataccttccc | 120 |
| cacagaactg  | gggtccggcc | tccttgacat  | gcagatttcc | accagaaga  | cagagaagga | 180 |
| gccagtgggtc | atggaatggg | ctgggggtcaa | agactgggtg | cctgggagct | gaggcagcca | 240 |
| ccgtttcagc  | ctggccagcc | ctctggaccc  | cgaggttggg | ccctactgtg | acacacctac | 300 |
| catgcggaca  | ctcttcaacc | tcctctggct  | tgccctggcc | tgacgccctg | ttcacactac | 360 |
| cctgtcaaaag | tcagatgcca | aaaaagccgc  | ctcaaagacg | ctgctggaga | agagtcagtt | 420 |
| ttcagataag  | ccggtgcaag | accgggggtt  | ggtggtgacg | gacctcaaag | ctgagagtgt | 480 |
| ggttcttgag  | catcgcagct | actgctcggc  | aaaggccccg | gacagacact | ttgctgggga | 540 |
| tgtactgggc  | tatgtcactc | catggaacag  | ccatggctac | gatgtcacca | aggtctttgg | 600 |
| gagcaagttc  | acacagatct | caccgtctg   | gctgcagctg | aagagacgtg | gccgtgagat | 660 |
| gtttgaggtc  | acgggcctcc | acgacgtgga  | ccaagggtgg | atgcgagctg | tcaggaagca | 720 |

|             |            |             |            |            |            |      |
|-------------|------------|-------------|------------|------------|------------|------|
| tgccaagggc  | ctgcacatag | tgccctcggt  | cctgtttgag | gactggactt | acgatgattt | 780  |
| cgggaacgtc  | ttagacagtg | aggatgagat  | agaggagctg | agcaagaccg | tggtccaggt | 840  |
| ggcaaagaac  | cagcatttcg | atggcttcgt  | ggtggaggtc | tggaaccagc | tgctaagcca | 900  |
| gaagcgcgtg  | accgaccagc | tgggcatggt  | cacgcacaag | gagtttgagc | agctggcccc | 960  |
| cgtgctggat  | ggtttcagcc | tcattgacct  | cgactactct | acagcgcctc | agcctggccc | 1020 |
| taatgcaccc  | ctgtcctggg | ttcgagcctg  | cgtccaggtc | ctggaccgga | agtccaagtg | 1080 |
| gcgaagcaaa  | atcctcctgg | ggctcaactt  | ctatggtatg | gactacgcga | cctccaagga | 1140 |
| tgcccgtgag  | cctgttgctg | gggccaggta  | catccagaca | ctgaaggacc | acaggccccg | 1200 |
| gatgggtggtg | gacagccagg | ycctcagagca | cttcttcgag | tacaagaaga | gccgcagtgg | 1260 |
| gaggcacgtc  | gtcttctacc | caaccctgaa  | gtccctgcag | gtgcggctgg | agctggcccc | 1320 |
| ggagctgggc  | gttggggctc | ctatctggga  | gctggggcag | ggcctggact | acttctacga | 1380 |
| cctgctctag  | gtgggcattg | cggcctccgc  | ggtggacgtg | ttcttttcta | agccatggag | 1440 |
| tgagtggagca | ggtgtgaaat | acaggccttc  | actccgttaa | aaaaaaaaaa | aaaaaaaaaa | 1500 |
| aaaaaaaaaa  | aaaaaa     |             |            |            |            | 1515 |

<210> 41  
 <211> 704  
 <212> DNA  
 <213> Homo sapiens

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 41   |            |            |            |            |            |     |
| aagatggtgg | cgcccagagc | ttcgtcttat | gctgctcccc | tgagagaggg | gtttccatca | 60  |
| accagttttg | caaggagtgc | aatgagagga | caaaggacat | caaggaaggc | attcctctgc | 120 |
| ctaccaagat | tttagtgaag | cctgacagga | catttgaaat | taagattgga | cagccactg  | 180 |
| tttctacttt | cctgaaggca | gcagctggga | ttgaaaagg  | ggcccggcaa | acagggaag  | 240 |
| aggtggcagg | cctggtgacc | ttgaagcatg | tgtatgagat | tgcccgcatc | aaagctcagg | 300 |
| atgaggcatt | tgccctgcag | gatgtacccc | tgtcgtctgt | tgtccgctcc | atcatcgggt | 360 |
| ctgcccgttc | tctgggcatt | cgcgtggtga | aggacctcag | ttcagaagag | cttgacgctt | 420 |
| tccagaagga | acgagccatc | ttcctggctg | ctcagaagga | ggcagatttg | gctgcccagg | 480 |
| aagaagctgc | caagaagtga | cccttgcccc | accaaactcc | agatttcaaa | ggaggtagtt | 540 |
| gcaaaagctg | tgcccaggga | gaggaaggag | gtcacaccaa | tatgatgatg | gttttcatga | 600 |
| ctttgaatga | tatatctttg | tacatctagc | tgtatcgagg | catcaggcct | gaataaacat | 660 |
| cctttcttaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaa       |            | 704 |

<210> 42  
 <211> 1094  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (196)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (226)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (302)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

<222> (596)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (952)  
 <223> n equals a,t,g, or c

<400> 42  
 ggcagctttc ttacaaaccc atcctttctga aatgttgctt caaattcatc ctctgctccc 60  
 cagtcccact attccacaca tactgttact gtttctttat cctactttct caattttgga 120  
 acatagttgc agttactgca ttgaatacct gtgggtttgc ctgttggtct gtctgtctct 180  
 gtgggttcttg taatantgga tcccagagat aaaatggaca gttgtnatgc acagttaatt 240  
 cagaaactag accttacttg ctgtgtgaaa taccaactaa attctcagtg aactcagctg 300  
 ancttttatct ccttttggtt ccccaattta taatttcagt tcaggcccag aaagatggaa 360  
 tcccagctaa gaaatacaag ttacaccctg tactagcagc ccatgtgtgc atgttcttta 420  
 agtgctcttg cagctatgtc atttatattg atttccctgt attattataa gcaaagcaaa 480  
 tttgagggaaa aaaaccata ataccacacc tcattttttt caagtaatag ggtcataagt 540  
 ctcatyctyc atataatatg ttgagtatgc agtatattat gtgttaggct ctggaanaggc 600  
 agaggttaga tcatgtwaca gatcatatck gattaggcag ataaacagta ttttaacctt 660  
 ttctttatta tatgtaactt gctttcaggt tttttaatgt tactattatg tctttaatat 720  
 attatcttta tttgtacttt tgtatacaga gtgattttcc ttttttaaaa aaaatttgtt 780  
 ctttaggatg gattccaaag atgtggaatc agtaggttta aggaatatgg atattttggc 840  
 tggcaagggt gctcacacct gtaatcccag cactttggga ggctgagggt ggtggatcac 900  
 ctgaagtcag gagttcgaga ccagcctgac caacatggcg aaaccctgtt tntactaaag 960  
 acacacwaa aatrrgcag tgggtggtggc atgtgcttgt agtcccactt agctactcga 1020  
 gaggctgagg caggagaatc gcttgaaccg gggaggcaga ggttgcagtg aggcaagatg 1080  
 gcacctctac actc 1094

<210> 43  
 <211> 1821  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1801)  
 <223> n equals a,t,g, or c

<400> 43  
 tggcttaggc catcaccctt cccttggtcg gaactactgg acagaccctt ttgagatgtg 60  
 cctgtggtgc tgtggagatg tgtgtagtgg tcttagctct ttgttgagct tgtgtgtgtg 120  
 ttgtgtagtc ttagctgtat gctgaaattg ggcggtgtgt ggagggttcc ttagctcttt 180  
 ggtgagattg tatctctatg tgtttgatc asctgaatgt tgctggaaat aaaaccttgg 240  
 tttgtmaagg ctcttttttg tgggaagtaa gtaggggaaa aggtctttga gggttcctag 300  
 gctcctttgt acaacaggaa aatgcctcaa agccttgctt cccagcaacc tggggctggt 360  
 tcccagtgcc tggctctgcc ccttcctggt tcttatctca aggcagagct tctgaatttc 420  
 aggccttcct tccagagccc tcttggtggc aggccttcct ttgctggagg aaggtacaca 480  
 ggggtgaagct gatgctgtac ttgggggatc tccttggect gttccaccaaa gtgagagaag 540  
 gtacttactc ttgtacctcc tgttcagcca ggtgcattaa cagacctccc tacagctgta 600  
 ggaactactg tcccagagct gaggcaagggt gatttctcag gtcatttggga gaacaagtgc 660  
 tttagtagta gtttaaaagta gtaactgcta ctgtatttag tgggggtggaa ttcagaagaa 720  
 atttgaagac cagatcatgg gtggtctgca tgtgaatgaa caggaaatgag ccggacagcc 780  
 tggctgtcat tgctttcttc ctccccattt ggaccttct ctgcccttac atttttgttt 840  
 ctccatctac caccatccac cagtctatct attaatctag caagaggaca agtaaaagggc 900  
 cctcttggtt tgattttgct tctttctttc tgtggaggat aactaagtgc cgactttgcc 960  
 ctatcctatt tggaaatccc taacagaatt gagttttcta ttaaggatcc aaaaagaaaa 1020

|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| acaaaatgct  | aatgaagcca  | tcagtcaagg  | gtcacatgcc  | aataaacaat | aaattttcca  | 1080 |
| gaagaaatga  | aatccaacta  | gacaaataaa  | gtagagctta  | tgaaatgggt | cagtaaggat  | 1140 |
| gagtttggtg  | ttttttgttt  | tgttttgttt  | tgktttttta  | aagacggagt | ctcgctctgt  | 1200 |
| cactcaggct  | ggagtgcagt  | ggtagatctt  | tggtcactg   | taacctccgc | ctcccgggtt  | 1260 |
| caagccattc  | tcctgcctca  | gtctcctgag  | tagctgggat  | tacaggtgcg | tgccaccatg  | 1320 |
| cctggctaata | ttttgtgttt  | ttagtagaga  | cagggtttca  | ccatgttggt | cgggctgggtc | 1380 |
| tcaaactcct  | gacctcttga  | tccgcctgcc  | ttggcctccc  | aaagtgatgg | gattacagat  | 1440 |
| gtgagccacc  | cgtgccctag  | ccaaggatga  | gattttttaa  | gtatgtttca | gttctgtgtc  | 1500 |
| atggttgga   | gacagagtag  | gaaggatatg  | gaaaagggtca | tggggaagca | gaggtgattc  | 1560 |
| atggctctgt  | gaatttgagg  | tgaatgggtc  | cttattgtct  | aggccacttg | tgaagaatat  | 1620 |
| gagtcagtta  | ttgccagcct  | tgggaatttac | ttctctagct  | tacaatggac | cttttgaact  | 1680 |
| ggaaaacacc  | ttgtctgcat  | tcacttttaa  | atgtcaaaac  | taatttttat | aataaatgtt  | 1740 |
| tattttcaca  | ttgaaaaaaa  | aaaaaaattt  | aaaaacycgg  | ggggggcccs | gwacccatt   | 1800 |
| ngcccctaag  | gggggggggtt | t           |             |            |             | 1821 |

&lt;210&gt; 44

&lt;211&gt; 1024

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 44

|             |             |            |             |             |            |      |
|-------------|-------------|------------|-------------|-------------|------------|------|
| ggggcacagt  | tgaagaagcg  | accgagggac | tgggagtcgt  | tagtgaggat  | gacgcggcat | 60   |
| ggcaagaact  | gcaccgcagg  | gccgtctaca | cctaccacga  | gaagaagaag  | gacacagcgg | 120  |
| cctcgggcta  | tgggaccag   | aacattcgac | tgagccggga  | tgccgtgaag  | gacttcgact | 180  |
| gctgttgtct  | ctccctgcag  | ccttgccacg | atcctgttgt  | cacccagat   | ggctacctgt | 240  |
| atgagcgtga  | ggccatcctg  | gagtacattc | tgaccagaa   | gaaggagatt  | gcccggcaga | 300  |
| tgaaggccta  | cgagaagcag  | cggggcacc  | ggcgcgagga  | gcagaaggag  | cttcagcggg | 360  |
| cggcctcgca  | ggaccatgtg  | cggggcttcc | tggagaagga  | gtcggctatc  | gtgagccggc | 420  |
| ccctcaaccc  | tttcacagcc  | aaggccctct | cgggcaccag  | cccagatgat  | gtccaacctg | 480  |
| ggcccagtg   | gggtcctcca  | agtaaggaca | aggacaaagt  | gctgcccagc  | ttctggatcc | 540  |
| cgtcgctgac  | gcccgaagcc  | aaggccacca | agctggagaa  | gccgtcccgc  | acggtgacct | 600  |
| gcccctatgtc | aggggaagccc | ctgcgcattg | cggacctgac  | gcccgtgcac  | ttcacaccgc | 660  |
| tagacagctc  | cgtggaccgc  | gtggggctca | tcaccgcag   | cgagcgctac  | gtgtgtgccg | 720  |
| tgaccgcgga  | cagcctgagc  | aacgccaccc | cctgcgctgt  | gctgcggccc  | tctggggctg | 780  |
| tggtcacctt  | cgaatgcgtg  | gagaagctga | ttcggaagga  | catggtggac  | cctgtgactg | 840  |
| gagacaaact  | cacagaccgc  | gacatcatcg | tgctgcagcg  | gggcgggtacc | gsttcgcggg | 900  |
| ctccggagtg  | aagctgcaag  | cggagaaatc | acggccgggtg | atgcaggcct  | gagtgtgtgc | 960  |
| gggagaccaa  | ataaacgggc  | ttgggtgcgc | aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa  | 1020 |
| aaaa        |             |            |             |             |            | 1024 |

&lt;210&gt; 45

&lt;211&gt; 983

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (976)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 45

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| cgacacggct | gcgagaagac | gacagaaggg | cccagaccgc | agccgtccag | gtctcagtgc  | 60  |
| tgtgcccccc | ccagagccta | gaggatgttt | catgggatcc | cagccacgcc | gggcatagga  | 120 |
| gcccctggga | acaagccgga | gctgtatgag | gaagtgaagt | tgtacaagaa | cgcccgaggag | 180 |
| agggagaagt | acgacaacat | ggcagagctg | tttgcggtgg | tgaagacaat | gcaagccctg  | 240 |
| gagaaggcct | acatcaagga | ctgtgtctcc | cccagcgagt | acactgcagc | ctgctcccgg  | 300 |



|             |             |             |            |            |             |     |
|-------------|-------------|-------------|------------|------------|-------------|-----|
| ctcctgggtcc | aatacaaaagc | tgcccttcagg | caggtccagg | gtcagaaaat | cagctctatt  | 360 |
| gacgaattct  | gccgcaagtt  | ccgcctggac  | tgcccgttg  | ccatggagcg | gatcaaggag  | 420 |
| gaccggccca  | tcaccatcaa  | ggacgacaag  | ggcaacctca | accgctgcat | cgcagacgtg  | 480 |
| gtctcgtctt  | tcatcacggg  | catggacaag  | ctgcgccttg | agatccgcgc | catggatgag  | 540 |
| atccagcccc  | acctgcgaga  | gctgatggag  | accatgcacc | gcatgagcca | cctccccacc  | 600 |
| gactttgagg  | gccgccagac  | ggtcagccag  | tggctgcaga | ccctgagcgg | catgtcggcg  | 660 |
| tcagatgagc  | tggacgactc  | acaggtgcgt  | cagatgctgt | tcgacctgga | gtcagcctac  | 720 |
| aacgccttca  | accgcttcct  | gcatgcctga  | gccccgggca | ctagcccttg | cacagaaggg  | 780 |
| cagagtctga  | ggcgatggct  | cctgggtccc  | tgtccgccac | acaggccgtg | gtcatccaca  | 840 |
| caactcactg  | tctgcagctg  | cctgtctggt  | gtctgtcttt | ggtgtcagaa | cttttggggc  | 900 |
| gggccccctc  | ccacaataaa  | gatgctctcc  | gaccttcaaa | aaaaaaaaaa | aaaaaaaaagr | 960 |
| kgsggcccgt  | ccccantccc  | ccc         |            |            |             | 983 |

&lt;210&gt; 46

&lt;211&gt; 2421

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 46

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ccggtgatac  | gctgccgctc  | cgccaataca  | atagagccak  | ccactaccag  | cagcctggcc  | 60   |
| ctcttctctc  | ttctccagag  | agaccaatcc  | agccgaactc  | ggggtttgcc  | tgaggagaag  | 120  |
| gaggaaagtga | ccatggacac  | aagtgaanaa  | agacctgaaa  | atgatgttcc  | agaacctccc  | 180  |
| atgcctattg  | cagaccaagt  | cagcaatgat  | gaccgcccgg  | agggcagtg   | tgaagtggag  | 240  |
| gagaagaaaag | agagctcgct  | gccccaatca  | ttcaagagga  | agatctccgt  | tgtctcagct  | 300  |
| accaagggggg | tgccagctgg  | aaacagtgc   | acagaggggg  | gccagcctgg  | tcggaacga   | 360  |
| cgctggggag  | ccagcacagc  | caccacacag  | aagaaacctt  | ccatcagtat  | caccactgaa  | 420  |
| tcactaaaga  | gcctcatccc  | cgacatcaaa  | cccctggcgg  | ggcaggaggc  | tgttgaggat  | 480  |
| cttcatgctg  | atgactctcg  | catctctgag  | gatgagacag  | agcgtaatgg  | cgatgatggg  | 540  |
| acccatgaca  | aggggctgaa  | aatatgccgg  | acagtcactc  | aggtagtacc  | tgcagagggc  | 600  |
| caggagaatg  | ggcagaggga  | agaagaggaa  | gaagagaagg  | aacctgaagc  | agaacctcct  | 660  |
| gtacctcccc  | aggtgtcagt  | agaggtggcc  | ttgcccccac  | ctgcagagca  | tgaagttaaag | 720  |
| aaagtgactt  | taggagatac  | cttaactcga  | cgttccatta  | gccagcagaa  | gtccggagtt  | 780  |
| tccattacca  | ttgatgacct  | agtccgaact  | gcccaggtgc  | cctccccacc  | ccggggcaag  | 840  |
| attagcaaca  | ttgtccatat  | ctccaatttg  | gtccgtcctt  | tcactttagg  | ccagctaaag  | 900  |
| gagttgttgg  | ggcgcacagg  | aaccttggtg  | gaagagccct  | tctggattga  | caagatcaaa  | 960  |
| tctcattgct  | ttgtaacgta  | ctcaacagta  | gaggaaagctg | ttgccaccgg  | cacagctctg  | 1020 |
| cacgggggtca | aatggcccca  | gtccaatccc  | aaattccctt  | gtgctgacta  | tgccgagcaa  | 1080 |
| gatgagctgg  | attatcaccc  | aggcctcttg  | gtggaccgtc  | cctctgaaac  | taagacagag  | 1140 |
| gagcagggaa  | taccacggcc  | cctgcacccc  | ccacccccac  | ccccgggtcca | gccaccacag  | 1200 |
| cacccccggg  | cagagcagcg  | ggagcaggaa  | cgggcagtg   | gggaacagtg  | ggcagaacgg  | 1260 |
| gaacgggaaa  | tggagcggcg  | ggagcggact  | cgatcagagc  | gtgaatggga  | tcgggacaaa  | 1320 |
| gttcgagaag  | ggccccgttc  | ccgatcaagg  | tcccgttrac  | gccgccgcaa  | ggaacgtgcg  | 1380 |
| aagtctaaaag | aaaagaagag  | tgagaagaaa  | gagaaagccc  | aggaggaacc  | acctgccaaag | 1440 |
| ctgctggatg  | accttttccg  | aaagaccaag  | gcagctccct  | gcatctattg  | gtctccactg  | 1500 |
| actgacagcc  | agatcggtca  | gaaagaggca  | gagcggggcg  | aacggggcaa  | ggagcgggag  | 1560 |
| aagcggcgaa  | aggagcaaga  | agaagaagag  | caaaaggagc  | gggagaagga  | agccgagcgg  | 1620 |
| gaacggaacc  | gacagctgga  | gagagagaaa  | cgtcggggagc | acagtccggga | gagggacagg  | 1680 |
| gagagagaga  | gagaaaggga  | gagggacagg  | ggggaccgag  | atcgggatag  | ggaaagggac  | 1740 |
| cgagaacgag  | gcagggaaaag | ggatcgcagg  | gacaccaagc  | gccacagcag  | aagccggagt  | 1800 |
| cggagcacac  | ctgtgcggga  | ccgggggtggg | cgccgctagc  | tgggaaaaca  | ctagagctgc  | 1860 |
| aggtaccagc  | cactcgggcc  | caggggggta  | tggccacaga  | gggataggca  | cagtctccac  | 1920 |
| caccttgagg  | ccaagggtct  | ttcacatcac  | ctatccctac  | atacatacca  | aatggaaaag  | 1980 |
| tggccatcct  | tttcccccca  | aacacacccc  | cttaacctat  | ctcttggggac | ttagcccagc  | 2040 |
| cctccctctc  | atttcccatt  | aagtctgaga  | ggcaagagct  | aggttaggca  | aggaggtggt  | 2100 |
| tggccagaga  | tggggaacag  | ccaggtgccc  | cagtctctctg | atttttccctc | catcctgctt  | 2160 |
| accacctccc  | tgggtactta  | cagccttctc  | ttgggaacag  | ccggggccag  | gactgggtca  | 2220 |
| cctatgagct  | gaatcagcat  | ctcctctctga | gtcccagggc  | ccctgcagtt  | cccagctctc  | 2280 |

|            |            |            |            |             |            |      |
|------------|------------|------------|------------|-------------|------------|------|
| tctgtcctgc | agcccttgcc | tctttccac  | aggttccact | ttatatccac  | cttttccttt | 2340 |
| tggtcaattt | ttatttttat | tttttttatt | attaaatgat | gtgggtctatg | gaaaaaaaaa | 2400 |
| taaaaatctg | acttagtttt | a          |            |             |            | 2421 |

<210> 47  
 <211> 840  
 <212> DNA  
 <213> Homo sapiens

|             |            |             |            |            |            |     |
|-------------|------------|-------------|------------|------------|------------|-----|
| <400> 47    |            |             |            |            |            |     |
| ctcaaaactcc | tgagctgaag | cgatctacct  | gcctcagcta | ggattacagg | tgtgagccac | 60  |
| cgcacccaac  | ctcaataagc | ktatttgata  | aaakatatgc | aagctccctt | tatkcacttt | 120 |
| tcattcagaa  | tgtttagtaa | tttgattgt   | ttttcagatt | ttcagcccaa | tatatctccy | 180 |
| tgccactgt   | gtcactgtat | tctacctawa  | catcatcacg | tgtttctgct | attggctgta | 240 |
| tgatggaaca  | ctgcgggtca | ttttcctgaa  | aactgccgat | agtgcataga | rtgctgggat | 300 |
| ggaaaccaga  | arctttgaat | tcaagccttg  | gttctgcctt | gtttttgctt | gggtggcctt | 360 |
| gagtcagcca  | catacctttt | aaaatctcaa  | tttattagaa | attattccaa | atcaaaatca | 420 |
| aatgagaagg  | tatatacaaa | agtgccttat  | cccacaataa | actattcaag | agagagcaaa | 480 |
| ggagaggaca  | tttactcaac | acctcctaaa  | aggcagccag | tgaaattagg | cattttattt | 540 |
| aatcctcctg  | gcaactctga | gagtaaagca  | ttattaatcc | cattttggct | gtttaaagaa | 600 |
| attatttgca  | ctagattcca | gctgtagttt  | agyttcagaa | aaaaaaatcc | tgagatgtga | 660 |
| attcacagct  | ttctgggttt | aaagcccaag  | ctctatcaca | tcatgctatt | attgttacat | 720 |
| tactgctagt  | tctatgaaaa | gaaatactaa  | tttatgaaat | acatcttatc | caaaaaaaaa | 780 |
| aaaaaaaaac  | tgggaggggg | ggcccgctacc | caaatcgccg | gatagtgatc | gtaaacatc  | 840 |

<210> 48  
 <211> 2432  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (593)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2049)  
 <223> n equals a,t,g, or c

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| <400> 48   |            |            |            |            |             |     |
| ggcacgaggg | ccggaacgct | gaggaagggc | ccgtcccggc | ttccccggcg | cgccatggag  | 60  |
| cccggggcgg | ttgcagaagc | cgtggagacg | ggtaggagg  | atgtgattat | ggaagctctg  | 120 |
| cggtcataca | accaggagca | ctcccagagc | ttcacgtttg | atgatgccca | acaggaggac  | 180 |
| cggaagagac | tggcggastg | ctggtctccg | tcctggaaca | gggcttgcca | ccctcccacc  | 240 |
| gtgtcatctg | gctgcagagt | gtccgaatcc | tgtcccggga | ccgcaactgc | ctggaccctg  | 300 |
| tcaccagccg | ccagagcctg | caggcaytag | cctgytatgy | tgacatctct | gtctctgagg  | 360 |
| ggctcgtccc | agagtccgca | gacatggatg | ttgtactgga | gtccctcaag | tgcctgtgca  | 420 |
| acctcgtgct | cagcagccct | gtggcacaga | tgctggcagc | agaggcccg  | ctagtgggtga | 480 |
| agctcacaga | gcgtgtgggg | ctgtaccgtg | agaggagctt | ccccacgat  | gtccagttct  | 540 |
| ttgacttgcg | gtcctctctc | ctgctaaccg | cactccgcac | cgatgtgcgc | canagctgtt  | 600 |
| tcaggagctg | aaaggagtgc | gcctgctaac | tgacacactg | gagctgacgc | tgggggtgac  | 660 |
| tcctgaaggg | aacccccac  | ccacgctcct | tccttcccaa | gagactgagc | gggccatgga  | 720 |
| gatcctcaaa | gtgctcttca | acatcacctt | ggactccatc | aagggggagg | tggacgagga  | 780 |
| agacgctgcc | ctttaccgac | acctggggac | ccttctccgg | cactgtgtga | tgatcgctac  | 840 |
| tgctggagac | cgcacagagg | agttccacgg | ccacgcagta | ascctcctgg | ggaacttgcc  | 900 |

|            |             |            |            |             |             |      |
|------------|-------------|------------|------------|-------------|-------------|------|
| cctcaagtgt | ctggatgttc  | tcctcaccct | ggagccacat | ggagactcca  | cggagttcat  | 960  |
| gggagtgaat | atggatgtga  | ttcgtgccct | cctcatcttc | ctagagaagc  | gtttgcacaa  | 1020 |
| gacacacagg | ctgaaggaga  | gtgtagctcc | cgtgctgagc | gtgctgactg  | aatgtgcccg  | 1080 |
| gatgcaccgc | ccagccagga  | agttcctgaa | ggcccaggtg | ctgccccctc  | tgccgggatgt | 1140 |
| gaggacacgg | cctgaggttg  | gggagatgct | gcggaacaag | cttgtccgcc  | tcattgacaca | 1200 |
| cctggacaca | gatgtgaaga  | gggtggctgc | cgagttcttg | tttgtcctgt  | gctctgagag  | 1260 |
| tgtgccccga | ttcatcaagt  | acacaggcta | tgggaatgct | gctggccttc  | tggtgccag   | 1320 |
| gggcctcatg | gcaggaggcg  | gcccaggggc | agtactcaga | ggatgaggac  | acagacacag  | 1380 |
| atgagtacaa | ggaagccaaa  | gccagcataa | accctgtgac | cgggaggggtg | gaggagaagc  | 1440 |
| cgcctaacc  | tatggagggc  | atgacagagg | agcagaagga | gcacgaggcc  | atgaagctgg  | 1500 |
| tgaccatgtt | tgacaagctc  | tccaggaaca | gagtcatcca | gccaatgggg  | atgagtcctc  | 1560 |
| ggggtcatct | tacgtccctg  | caggatgcca | tgtgcgagac | tatggagcag  | cagctctcct  | 1620 |
| cggaccctga | ctcggaccct  | gactgaggat | ggcagctctt | ctgctcccc   | atcaggactg  | 1680 |
| gtgctgcttc | cagagacttc  | cctgggggtg | caacctgggg | aagccacatc  | ccactggatc  | 1740 |
| cacaccgcgc | cccacttctc  | catcttagaa | accccttctc | ttgactcccg  | ttctgttcat  | 1800 |
| gatttgcttc | tgggtccagtt | tctcatctct | ggactgcaac | ggtcttcttg  | tgctagaact  | 1860 |
| caggctcagc | ctcgaattcc  | acagacgaag | tactttcttt | tgtctgcgcc  | aagaggaatg  | 1920 |
| tgttcagaag | ctgctgcctg  | agggcagggc | ctacctgggc | acacagaaga  | gcataatggga | 1980 |
| gggcaggggt | ttgggtgtgg  | gtgcacacaa | agcaagcacc | atctgggatt  | ggcacactgg  | 2040 |
| cagagcmant | gtkttgggg   | atgtgctgca | cttcccaggg | agaaaacctg  | tcagaacttt  | 2100 |
| ccatacagag | atatcagaac  | acacccttcc | aaggatgta  | tgtctgttg   | ttcctgtcct  | 2160 |
| gtcttcactg | agcgagggc   | tggaggcctc | ttagacattc | tccttggtcc  | tcgttcagct  | 2220 |
| gccactgta  | gtatccacag  | tgcccgagtt | ctcgctgggt | ttggcaatta  | aacctccttc  | 2280 |
| ctactggttt | agactacact  | tacaacaagg | aaaatgcccc | tcgtgtgacc  | atagattgag  | 2340 |
| atttatacca | cataccacac  | atagccacag | aaacatcatc | ttgaaataaa  | gaagagtttt  | 2400 |
| ggacaaaaaa | aaaaaaaaaa  | aaaaaaaaaa | aa         |             |             | 2432 |

&lt;210&gt; 49

&lt;211&gt; 1742

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (570)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 49

|             |             |            |            |             |             |     |
|-------------|-------------|------------|------------|-------------|-------------|-----|
| gtcctgcagg  | agctgcacgc  | ggccgaggtg | cgcangaaca | aggagcagcg  | agaagagatg  | 60  |
| tcgggctaag  | ggcccggagc  | grggggcgcc | catcctgcga | cggaaacacgt | tcgggttttg  | 120 |
| gttttgtttc  | gttcacctct  | gtctagatgc | aacttttggt | cctcctcccc  | cacccagacc  | 180 |
| cccagcttca  | tgtttctctt  | ccgactcag  | ccgcccctgc | ctgtcctcgt  | ggtgagtcgc  | 240 |
| tgaccacggc  | ttccccctgca | ggagccgcgc | ggcgtgraga | cgcggtccct  | cgggtgcagac | 300 |
| accaggccgg  | gcgcggctgg  | gtcccccggg | ggcctgtgta | gagaggtggy  | ggtgaccgtg  | 360 |
| gtaaacccag  | ggcgggtggc  | tgggacrcg  | ggtccttacg | ctgggctgtc  | tggtcagcac  | 420 |
| gtgcagggtca | gggcagggtcc | tctgagccgg | cgcctctggc | cagcaggcga  | ggctacagta  | 480 |
| cctgtctgtct | ttcccagggg  | aaggggctcc | ccatgaggra | ggggcgacgg  | gggagggggg  | 540 |
| tgatgtgcgc  | tgggaagcct  | gcktgtgcan | cgggtgcttg | ttgaactggc  | aggcgggtgg  | 600 |
| gtgggggctg  | cagctttcct  | taatgtgggt | gcacaggggt | cctctragac  | cacctggcgt  | 660 |
| gaggtggaca  | ccctgggcct  | tcctggaagc | ctgcagttgg | gggcctgccc  | tgagtctgct  | 720 |
| ggggagtggt  | cattctctgc  | cagggaacca | tgagcaggct | gcattggtcta | gaggttgtgg  | 780 |
| gcagcatgga  | cagtccecca  | ctcagaagtg | caagagttcc | aaagagcctc  | tggcccaggc  | 840 |

|            |            |             |             |            |            |      |
|------------|------------|-------------|-------------|------------|------------|------|
| ccctccgtgg | gacagccccg | ccgccccctcc | ccaccagggc  | tttgagatg  | tccttgaaag | 900  |
| accacccta  | gagccctttg | gagtgcctggc | ccctcctgtg  | ccctctgccc | tggtggaagc | 960  |
| ggcascacaa | gtcctcctca | gggagcccca  | agggggattt  | tktgggaccg | ctgcccacag | 1020 |
| atccaggtgt | tggaaggcca | gcgggtaagg  | ttcccaagcc  | agccccaaca | cccttcccac | 1080 |
| ttggacccca | gagggggctg | tgggtggagg  | cctgactcca  | ggcctctcct | gcccacaccc | 1140 |
| tctgggctga | gttccttctt | tcccttggac  | gcccagtgtc  | ggccttggag | gacggtcagc | 1200 |
| tggaggatgg | cgggtggggg | ggctgtcttt  | gtaccactgc  | agcatcccc  | acttctccac | 1260 |
| ggaagcccca | tcccaaagct | gctgcctggc  | cccttgctgt  | aaagtgtgaa | gggggagggt | 1320 |
| gagttctctt | aggaccacga | gccaggggcc  | tcaacttcca  | tcctgcggga | ggccttggcc | 1380 |
| gggcactgcc | agtgtcttcc | agagccacac  | ccagggaacca | cgggaggatc | ctgacccttg | 1440 |
| cagggctcag | gggtcagcag | ggaccactct  | ccccatctcc  | ctctccccac | caagacagcc | 1500 |
| ccagaaggag | cagccagctg | ggatgggaac  | ccaaggctgt  | ccacatctgg | cttttgtggg | 1560 |
| actcagaaag | ggagcagaaa | ctgagggctg  | ggatattcct  | catggtggca | gcgctcatag | 1620 |
| cgaagccta  | ctgtaatatg | cacccatctc  | atccacgtag  | taaagtgaac | ttaaaaattc | 1680 |
| aatcaaatga | acaattaaat | aaacacctgt  | gtgtttaaga  | aaaaaaaaa  | aaaaaaactg | 1740 |
| cg         |            |             |             |            |            | 1742 |

&lt;210&gt; 50

&lt;211&gt; 1487

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1486)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 50

|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| ggcacgagcc  | tccgcgaact  | gtggagtcgg  | cggagggctg  | gaatcagcgt | gggctccagg  | 60   |
| tcgctggcag  | ccgggtggca  | gaactcttcc  | gaggctcctt  | gggaagaagc | tacacccgag  | 120  |
| ggagccggat  | gggcctcgaa  | aacctggccc  | gctctggttc  | tgtaccattg | caaggggaac  | 180  |
| cgtaaactga  | gctttttctaa | cgtgggtttc  | tgccaagtac  | ttttccagct | gcccccttcc  | 240  |
| ccccagcaca  | caggagagcc  | tctgtgtagc  | cagcgcttga  | cagtcgttag | gtagggttgta | 300  |
| ctgtgtaggg  | aggagctcaa  | gatcatgaat  | ggttgtcaca  | ggagaaagcg | gttgcatctt  | 360  |
| tgcaaaaacta | tatacctgct  | gtgggtttgtg | ttttcttttc  | tgctgagtaa | tgaagttgta  | 420  |
| agttcacact  | ggcacattct  | cagggctgtg  | cagattattt  | gcactttatt | tcatagggtgr | 480  |
| ataagtgtct  | tttagctttc  | tttgtatatt  | gagttgcttt  | tgaattgctt | cccatatttt  | 540  |
| tatttcatac  | aaactgaaca  | attgtggccc  | ctctatttta  | tttataaagg | ttcagtgtat  | 600  |
| ctttgcctgc  | ctacatcaat  | ctgcaaggga  | gttgacagaaa | gcctcatggt | catcgagccg  | 660  |
| tgagtcacaa  | ccaatttcta  | agctgttata  | acaaaaaagt  | gtttgctttt | tttcacaagt  | 720  |
| aactttaaaa  | gtgtagttaa  | gaaagaaaac  | attttcaata  | aaaagacact | acattaatcc  | 780  |
| tggatgcttg  | caaataccta  | aatmtattcc  | tcctctagcg  | ttgcacagct | ctgtgttgta  | 840  |
| tacacagact  | agctttaaaa  | tttgtcacat  | accactttac  | ctttactttt | atgtatcatt  | 900  |
| cccccgactt  | ccttactgca  | ggtgtgggca  | agaaaaactt  | tcctttaaca | cttttcaaca  | 960  |
| gcgggcataa  | aattctgcag  | ctgaggtctt  | gaagaatgca  | gatgggtaca | gtatgtgttg  | 1020 |
| gagctcacag  | tgtgtattga  | ctaacctagt  | tccttttttg  | cttttttttg | tattgtcttg  | 1080 |
| ttaaaagtga  | ctcccaggta  | gcaactctct  | tttttaaggg  | tgggaacgaa | agggacgtag  | 1140 |
| gaagaataga  | tctaagattat | ttaacagctc  | tcgatagagt  | ttgaaagctt | tcttcttcat  | 1200 |
| tcaatttttg  | gcaaaatact  | gcctctgcat  | tgttcataaa  | caaaaagatt | agattaataa  | 1260 |
| gtagcttttg  | ttgggtggaaa | ttaccagctc  | tataagtcac  | ccttggtggg | tcattggacct | 1320 |
| ctgattagct  | tgggttttgc  | agtctcattg  | ccacatgtat  | atgtggagcc | aatggccttt  | 1380 |
| tgggtgctcag | ctgtttacgt  | ctgactcctt  | gacttctttg  | gtacagtgat | ggagtcagat  | 1440 |
| ctcattaagt  | gtgattctcc  | atggatataa  | ccagccccaa  | aaaaaang   |             | 1487 |

&lt;210&gt; 51

&lt;211&gt; 1328

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

|             |             |            |            |             |             |      |
|-------------|-------------|------------|------------|-------------|-------------|------|
| ggcagcagct  | cgtgccgaat  | tgggcacgag | agaagatttg | aagaagccag  | atccagcttc  | 60   |
| cctgcgggct  | gcttcttggt  | gggaaggga  | aaagaggga  | gcctgtaaga  | actgcacctg  | 120  |
| tggccttgcc  | gaagaactgg  | aaaaagagaa | gtcaaggga  | cagatgagct  | cccaacccaa  | 180  |
| gtcagcttgt  | ggaaactgct  | acctgggcga | tgccttccgc | tgtgccagct  | gccccctacct | 240  |
| tgggatgcc   | gccttcaaac  | ctggggaaaa | gggtgctctg | agtgatagca  | atcttcatga  | 300  |
| tgccctaggag | gttcctgaca  | tgggacccat | ctgctcctcc | agccaaactcc | tgtccctcac  | 360  |
| atcccaccat  | gggtggctcct | cccacctcct | ctggatttgt | tcactctgag  | atctgtttgc  | 420  |
| agagtgggtg  | cttagcagac  | agagtgaagc | tggctggggg | gcacagtggg  | gtgtagtgt   | 480  |
| gctgtgtatc  | aaaagaccaa  | ggtattatgg | gacctgggtt | cagaatggga  | tgggtttctt  | 540  |
| cacctcatgt  | taagagaagg  | gagtgtgtcc | tgaagaagcc | cttcttctga  | tgtaaaatg   | 600  |
| ctgaccagaa  | cgctcttgag  | cccaggcatc | gttgagcatt | aacactctgt  | gacagagctg  | 660  |
| cagacccctg  | ccttgagtct  | catctcagca | atgctgccac | cctcttgtct  | ttcagagttg  | 720  |
| ttagtttact  | ccattctttg  | tgacacgagt | caagtggctc | acaacctcct  | cagggcacca  | 780  |
| gaggactcac  | tcactgggtg  | ctgtgatgat | atccagtgtc | cctctgcccc  | cttccatccc  | 840  |
| caaccacatt  | tgactgtagc  | attgcatctg | tgtcctgttg | tcattttatgt | taaccttcag  | 900  |
| gtattaaact  | tgctgcatat  | cttgacatat | cttgagattc | tgcatgtctt  | gtaaagagag  | 960  |
| gggatgtgca  | ttgtgtgtg   | atgttgata  | gtcatccacg | ctcagtttgg  | accattggag  | 1020 |
| gaacttagtg  | tcacgcacaa  | atggggctat | tcctacgctt | agaatagggc  | ttgtctgccc  | 1080 |
| actttagaag  | agtcccaggt  | tggtagcat  | ttagaggga  | gcagggcaga  | actctgaacg  | 1140 |
| acaatacgtc  | tctctgagca  | gagaccctt  | tgttcttggt | atccacccat  | atggacttgg  | 1200 |
| aatcaatctt  | gccaaatatt  | tggagagatt | gtgtggattt | aagagacctg  | gatttttata  | 1260 |
| ttttaccagt  | aaataaaagt  | tttcattgat | atctgtcctt | gaaaaaaaaa  | aaaaaaaaaa  | 1320 |
| aaactcga    |             |            |            |             |             | 1328 |

&lt;210&gt; 52

&lt;211&gt; 1856

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 52

|            |            |            |             |            |             |      |
|------------|------------|------------|-------------|------------|-------------|------|
| gaattcggca | cgagctctgc | aacattgcaa | atgaacttgc  | agccgagggg | tccgctgccc  | 60   |
| cctagattaa | attccccggg | ctgaaactga | gttgagatt   | tacaatatca | tatttttaaat | 120  |
| tgctgtcttc | aattaaacca | tttatgacca | taactaattt  | tcaggatgtc | gatgcatgct  | 180  |
| tttccaggcc | ttccttcttt | gtacaaaagt | aatgtccat   | aaagcgtttc | acttatattc  | 240  |
| ttcaaacatg | atgctaattt | aaattaatta | cttctatga   | tatgttatta | ttcctatgat  | 300  |
| tttgccactg | ttattagtgc | tctcaaaaat | acatctaggg  | aagaggatta | ttttaagtra  | 360  |
| tttgattatc | tttctatctc | ttttatttat | ttctcattta  | cttaagaaat | tcgttccatt  | 420  |
| ggttggcatt | gatacagtaa | atttgtaaat | gaggagacaa  | tataaaaaat | ctaaattact  | 480  |
| tgtgcttaat | gactgtagca | gaatsccttt | tctctaaatc  | agattgtctt | tcttgagttt  | 540  |
| tagtttgata | gatttgcaag | ctatgctgct | tccatgaagt  | tagctgcgct | ggtagggaacg | 600  |
| caggcttctt | tgtctctggg | tgtagcttgc | atgatcgccc  | cattaggcag | acaacgtagc  | 660  |
| cggagatcac | aaatcaggcc | cttggtgtag | ttgctagtgt  | gtggaggtgc | agagaggttg  | 720  |
| gcagaaactg | acctcactgg | gcaaggggtg | ccatggacct  | gattctttaa | tgactctat   | 780  |
| gtgttcagga | agccacaggc | catatttgac | tctgagaaa   | aaaacaagag | gaaaaacccc  | 840  |
| acaaagtata | acaaccctt  | aagatacatc | tattttaaag  | tgaaattaat | ttttcagttt  | 900  |
| ataccattgg | ccaattacaa | gataaaaatg | ttcaatttct  | ttaagaatcc | tttgttgact  | 960  |
| tgtcttttca | tctcttgcta | tttatatttg | tcaactgttag | tcaacaaagt | cttatttgct  | 1020 |
| gaggaaggac | tttgctgcac | ttactgtacc | acatcaaaac  | ctggggaggg | tgggtgttaa  | 1080 |
| ctttttaaaa | aatgttatcc | tgattataac | aataatattg  | gcttttttca | tgaaaagagc  | 1140 |
| gccaccttgc | aagggttagt | gagatttatg | gaagttgaat  | acctaagcag | gaattgctgc  | 1200 |
| tagctccaaa | aatttgcgaa | gcaaaagcta | gccccaatg   | gtttggaagt | ttgaaactga  | 1260 |
| ttaacagatt | tgcatttgaa | gtgactccag | acattaggtc  | cagacattag | ttaaaaatag  | 1320 |
| aaagaggaa  | aaagacatct | yttctctcta | gaaaagataa  | caccrcaatt | aataatcctt  | 1380 |

|            |            |            |            |             |            |      |
|------------|------------|------------|------------|-------------|------------|------|
| cccactttca | ttgagatcag | cttgtctgat | aacctgatat | gagtgtgata  | atgataaaca | 1440 |
| tgataaatag | ggtacttttg | taattttgct | ggtgcattta | agaagatagt  | aaakgatgag | 1500 |
| ttcayctttt | ctycgaacat | ycctatycct | agatgtagtt | tacctcaa    | tgggaattat | 1560 |
| aactgtccta | atTTTTgttg | tgtaccctga | tgcccccttt | gctttaatac  | ccacagtgtg | 1620 |
| acaattaaat | atcacactat | gacatatgat | ttaagtagga | tattttaaaag | ataaatttta | 1680 |
| ggggtaaagt | tttacttcaa | aatgactcca | tatttcaa   | atctgttttag | actgtgaagg | 1740 |
| ccaaataatt | tttaagaaaa | catttgaaga | gtagtgtgtt | tgcatttgtg  | aataatctta | 1800 |
| ctcacagcaa | gtaaacgtaa | taaaagccaa | catttaagcc | aaaaaaaaa   | aaaaaa     | 1856 |

<210> 53  
 <211> 1558  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (17)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1514)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1551)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1556)  
 <223> n equals a,t,g, or c

|            |             |             |            |             |            |      |
|------------|-------------|-------------|------------|-------------|------------|------|
| <400> 53   |             |             |            |             |            |      |
| tggttatcca | ttcctgnaat  | tactttactt  | aggataatgg | cctccagctc  | cgtccaagtt | 60   |
| gtgcaaaaag | gtattatttc  | gttccttttt  | gtggctgagt | agtattccat  | ggtgtatata | 120  |
| taccacattt | tctttatoca  | ctcattgctt  | gatgggcagt | taggttggtt  | ccacatcttt | 180  |
| gcaattgtga | gttgtgctgc  | tccagatata  | atctttaact | cctttgcctt  | ctccacatac | 240  |
| atttccaagt | cctgttcatt  | ctacctcaa   | aatgtatctt | gtatccattc  | atctctctcc | 300  |
| atcttcaatc | tatttcaatg  | ccccatcatc  | tcttgcatgg | aggagtgtaa  | taattggcta | 360  |
| actggcctgt | tcttacattt  | taaaatcaaa  | agatgtgaca | ggtgaaatgc  | ctatttcagt | 420  |
| gtccattgat | ggttctgctt  | acacaccacc  | tggctgcctg | gtgtcgagc   | ggcagagttg | 480  |
| agcagtgatg | aaaagactgc  | ttggcccttt  | acagggaaag | caggtccact  | gtggcctgtg | 540  |
| aggacgagag | ctctgggcag  | gctcggacac  | tggcagaccc | tggctcctggc | tggccaaggc | 600  |
| agcagggtat | gtgtttcggg  | tcaactcacag | ggctcagcac | cactcctcat  | ggcttcctta | 660  |
| ctgtttcggc | agaggctgac  | cgcggctga   | ttgagtccct | ctcccagatg  | ctgtccatgg | 720  |
| gcttctctga | tgaaggcggc  | tggctcacca  | ggctcctgca | gaccaagaac  | tatgacatcg | 780  |
| gagcggctct | ggacaccatc  | cagtattcaa  | agcatccccc | gccgttgatg  | ccacttttgc | 840  |
| ccacctcttc | tgcgtgcccc  | tcttctgtct  | catagttgtg | ttaagcttgc  | gtagaattgc | 900  |
| aggtctctgt | acgggcccagt | ttctctgcct  | tcttccagga | tcaggggtta  | gggtgcaaga | 960  |
| agccatttag | ggcagcaaaa  | caagtgcac   | gaagggaggg | tccctgtgtg  | tgtgtgtgct | 1020 |
| gatgtttcct | gggtgcccctg | gctccttgca  | gcagggctgg | gcctgcgaga  | cccaaggctc | 1080 |
| actgcagcgc | gctcctgacc  | cctccctgca  | ggggctacgt | tagcagccca  | gcacatagct | 1140 |
| tgcctaattg | ctttcacttt  | ctcttttgtt  | ttaaatgact | cataggtccc  | tgacatttag | 1200 |
| ttgattattt | tctgctacag  | acctgggtaca | ctctgatttt | agataaagta  | agcctaggtg | 1260 |
| ttgtcagcag | gcaggctggg  | gaggccagtg  | ttgtgggctt | cctgctggga  | ctgagaaggc | 1320 |

|             |            |            |            |            |            |      |
|-------------|------------|------------|------------|------------|------------|------|
| tcaacgaaggg | catccgcaat | gttggtttca | ctgagagctg | cctcctgggc | tcttcaccac | 1380 |
| tgtagttctc  | tcattttcaa | accatcagct | gcttttaaaa | taagatctct | ttgtagccat | 1440 |
| cctgttaaatt | ttgtaaacia | tctaattaaa | tggcatcagc | actttaacca | aaaaaaaaaa | 1500 |
| aaaaaaaaaa  | aaaaaaaaaa | aaaagggggc | cgctctagag | gtccaagtta | ngacnggg   | 1558 |

<210> 54  
<211> 948  
<212> DNA  
<213> Homo sapiens

|             |             |
|-------------|-------------|
| <400> 54    |             |
| taaaaatcat  | gctctgtacc  |
| gaactactgg  | gatccctaaa  |
| ccaggctctt  | tctgcagwca  |
| ggccgtcaga  | cttgataaca  |
| aagmtcggaa  | tccagttcct  |
| ttccgggata  | ccggscaaac  |
| tgtagcgccc  | ccaaccgagc  |
| caccgcccc   | gctctgacaa  |
| tccgcgggg   | gattcagtc   |
| acagaccct   | ccctttcttc  |
| ctcctgtttt  | ttgcaagtac  |
| tgctaatacc  | agaacctttc  |
| aggacccttc  | tccctgggat  |
| acccatcccc  | gcccctgggc  |
| ccccgctccc  | cgctcccctc  |
| gaacttctga  | aagacaatat  |
| atcctcaccg  | tagtcatcat  |
| gtccggcccc  | actctgcgcc  |
| ccaatgggag  | ccctgcacac  |
| cgccctccac  | gaacgtctcg  |
| tccaaaaccc  | acacccccag  |
| gcccggaccct | cagtcgctcc  |
| tggtccctaa  | aacccccgct  |
| ccaggctcgg  | aggctccgct  |
| tttggtggct  | caggcctcgc  |
| ggggtagtaa  | ggsccccaca  |
| caggatctct  | cctattttct  |
| atttgaggac  | atttggggaag |
| cctgtaaacc  | ctctgtaaat  |
| agggaatcc   | aggctatgga  |
| ccttggtctg  | atctgtgtgt  |
| taagagact   | tagttgaaaa  |
| aaaaaaaaaa  |             |

<210> 55  
<211> 990  
<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (751)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (879)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (888)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (897)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (899)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (901)

<223> n equals a,t,g, or c

<400> 55

|            |             |            |             |             |             |     |
|------------|-------------|------------|-------------|-------------|-------------|-----|
| ggggaactgc | agtgacagca  | ggagtaagag | tgggaggcag  | gacagagctg  | ggacacaggt  | 60  |
| atggagaggg | ggttcagcga  | gcctagagag | ggcagactat  | caggggtgccg | gcggtgagaa  | 120 |
| tccagggaga | ggagcggaaa  | cagaagaggg | gcagaagacc  | ggggcacttg  | tgggttgacg  | 180 |
| agccctcag  | ccatgttggg  | agccaagcca | cactggctac  | caggtcccct  | acacagtccc  | 240 |
| gggtgcctt  | tggttctggt  | gcttctggcc | ctggggggccg | ggtggggcca  | ggaggggtca  | 300 |
| gagcccgtcc | tgctggaggg  | ggagtgcctg | gtggtctgtg  | agcctggccg  | agctgctgca  | 360 |
| ggggggcccg | ggggagcagc  | cctgggagag | gcaccccctg  | ggcgagtggc  | atttgytgcg  | 420 |
| gtccgaagcc | accaccatga  | gccagcaggg | gaaaccggca  | atggcaccag  | tggggccatc  | 480 |
| tacttcgacc | aggtcctggt  | gaacgagggc | ggtggctttg  | accgggcctc  | tggctccttc  | 540 |
| gtagcccctg | tccgggggtg  | ctacagcttc | cggttccatg  | tggtgaaggt  | gtacaaccgc  | 600 |
| caaaactgtc | aggtgagcct  | gatgctgaac | acgtggcctg  | tcatctcagc  | ctttgccaat  | 660 |
| gatcctgacg | tgaccgggga  | ggcagccacc | agctctgtgc  | tactgccctt  | ggaccctggg  | 720 |
| gaccgagtgt | ctctgcgcct  | gcgtcggggg | naatctactg  | ggtgggttga  | aataactcaag | 780 |
| tttctctggc | ttcctcatct  | tccctctctg | aaggacccaa  | gtctttcaag  | cacaagaatc  | 840 |
| cagcccttga | caactttctt  | ctgccctctc | ttgccccana  | aacagcanaa  | gcagganana  | 900 |
| nactccctct | ggctcctatc  | ccacctcttt | gcatgggaac  | ctgtgccaaa  | cacccaagtt  | 960 |
| taagaaaaaa | ataaaaactgt | ggcatctcca |             |             |             | 990 |

<210> 56

<211> 1603

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (328)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (336)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (341)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (788)

<223> n equals a,t,g, or c

<400> 56

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ggtcgaccca | cgcgtccggc | ccgccggctc | cggagcggct | ctgccttccc | gagcgcggga | 60  |
| ccgcgccctg | ggggaggagg | gcgaacgacg | cggcgatggc | tccgcgggca | ctcccggggg | 120 |
| ccgcgcctct | agccgctgct | gtcttcgtgg | gaggcgccgt | gagttcgccg | ctggtggctc | 180 |
| cggacaatgg | gagcagccgc | acattgcact | ccagaacaga | gacgaccccg | tcgcccagca | 240 |
| acgatactgg | gaatggacac | ccagaatata | ttgcatacgc | gcttgtccct | gtgttcttta | 300 |



|             |             |            |             |             |            |      |
|-------------|-------------|------------|-------------|-------------|------------|------|
| tcattgggtct | ctttggcgctc | ctcatttngc | camctngctt  | naagaagaaa  | ggctatcggt | 360  |
| gtacaacaga  | agcagagcaa  | gatatcgaag | aagaaaaagg  | ttgaaaagwt  | agrattgaat | 420  |
| gacagtgtga  | atgaaaacag  | tgacactgtt | gggcaaatcg  | tccactacat  | catgaaaaat | 480  |
| gaagcgaatg  | ctgatgtytt  | aaaggcgatg | gtagcagata  | acagcctgta  | tgatcctgaa | 540  |
| agccccgtga  | cccccagcac  | accagggagc | ccgccagtga  | gtcctgggct  | ttgtcaccag | 600  |
| gggggacgcc  | agggaaagcac | gtctgtggcc | atcatctgca  | tacgggtgggc | ggtgtwgtcg | 660  |
| agagggatgt  | gtgtcatcgg  | tgtaggcaca | agcgggtggca | ctttataaag  | cccactaaca | 720  |
| agtccagaga  | gagcagacca  | cggcgccaag | gcgaggtcac  | ggtcctttct  | gttggcagat | 780  |
| ttagagtnac  | aaaagtggag  | cacaagtcaa | accagaagga  | acggagaagc  | ctgatgtctg | 840  |
| ttagtggggc  | tgaaccgctc  | aatggggagg | tgccggcaac  | acctgtgaag  | agagaacgca | 900  |
| gtggcacaga  | gtagcagggtg | agccgtgggt | ttgggtgacat | tgggggcaga  | gtggtgcagg | 960  |
| gtgaggagaa  | ggtacttggg  | gcctcccagg | tgctgtggca  | gcataaggat  | ggtatttgac | 1020 |
| agggaagtgg  | gagagctttc  | cttgacccag | gaagactgag  | ggggactgaa  | catgattact | 1080 |
| tgtctgccta  | gagcttcttg  | taaagaagtc | acaaacttag  | tgcttccagg  | ggcttggctg | 1140 |
| tgtgataatg  | aggatagagg  | attacttgtg | aggcaatgtg  | gcattgggtgg | gattgtggca | 1200 |
| aactagaatt  | cacatcaccc  | accatatagg | gcttgcatta  | ccacgaggca  | gaaagcacct | 1260 |
| agtgttgctg  | catcttctta  | cgcaaaaaag | acaaaatcca  | gacttctaaa  | atgtaaaatc | 1320 |
| actgattttc  | gatattggca  | gcttactttt | tttttttaaa  | caaccatgca  | ggccaaatga | 1380 |
| cttgtaactc  | tgtaccatt   | tttaggtaaa | ctgtgacttg  | aaaaagtctg  | gagcaaacaa | 1440 |
| accaatgctt  | tttcttttta  | ttctgttggz | aaccagtttt  | ctttgtgtca  | cagttytgaa | 1500 |
| acctcaatac  | gaatatttct  | cttcccacca | aatattttga  | ggcaattgaa  | aagccacagt | 1560 |
| gattttatttc | ttgatattggc | aattttaatt | ttgcaagaca  | att         |            | 1603 |

&lt;210&gt; 57

&lt;211&gt; 1052

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (250)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1051)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1052)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 57

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| tacagctcag | gatgcctgta  | acattgtcat | ctctgggctt | ctgggtcctg | cttagcctgc | 60  |
| tttttccctg | gaggactgac  | cagggatgcg | gccagcaac  | atgttactaa | atcatactct | 120 |
| cctccctacc | tttcccagac  | ctctcactcc | tgcttgggtg | tccaaccctg | tctgtggcca | 180 |
| gagtatacat | tttggaaacct | cttcgaggcc | atcctgcagt | tccagatgaa | ccatagcgtg | 240 |
| cttcagcagn | aaggcccag   | acatgtatgc | agaggagcgg | aagaggcagc | agctggagag | 300 |
| ggaccaggct | acagtacag   | agcagctgct | gcgagagggg | ctccaagcca | gtggggacgc | 360 |
| ccagctccga | aggacacgct  | tgcaaaaact | ctcgccagga | cgggaagagc | gagtccaagg | 420 |
| cttctctgag | gccttggaa   | tcaagcgagc | tgactggctg | gcccgtctgg | gcaactgcac | 480 |
| agcctgaatg | aggctggcca  | cctgccactt | tgccctgccc | tctgcctcca | gggtccmct  | 540 |
| myccttcctt | ttcttgggtg  | aaggcacctc | ctttcctgat | aatgaatggt | gttccctttg | 600 |
| cttgggtggg | gagcccccca  | ggccagggtt | gctggccata | gatacctttg | gggtgcctgr | 660 |
| gacaggctcc | tgaggaggat  | tgagggtgaa | agtctcccac | gagtacacta | aacctaggtc | 720 |
| tggtcaccaa | taggggttgg  | agagcaaaag | gccacaactc | atcagctgcc | tgtctcttag | 780 |

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| atgcactttc | tttttccacc | agcacatcct | tcaacacaca | gaatttcagg | gaagagttct | 840  |
| ccccaaaacc | ctagctcttt | acccttccat | tttagccttc | caccagctt  | ccacaaaaga | 900  |
| tttggctcta | ccttgatct  | gctagtaa   | aactaatagg | caggcagtta | tttgggtaag | 960  |
| gaaaaaagg  | gtgggagaga | cagaaaattt | gccactgct  | gctcctccc  | ttggstytc  | 1020 |
| acctgggatt | tgctattgaa | tctctaccct | nn         |            |            | 1052 |

<210> 58  
 <211> 814  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (3)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (32)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (751)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (770)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (784)  
 <223> n equals a,t,g, or c

|            |  |
|------------|--|
| <400> 58   |  |
| acncgntggc | ggccgctcta gaactagggg anccccggg ctgcaggaat tcggcacgag 60   |
| catagacttt | taaactggta cggttcttag agatggtcct tggccttctg ttgttgttgt 120 |
| kgtttttttc | tttttcttct tctccttctc cttcttcttc tcttctcctt ctttcttctt 180 |
| ttttttttca | gagtcctgct ctgtcaccaa gactggagtg aagtgatgtg atctcggtt 240  |
| actgcaacct | gggaggcaga ggttgacgtg agtcgagatg gtgccattgc tctcggttgg 300 |
| gcaacaagag | tgaaactctt gtctcaaaaa aaaaaaaaaa atgaggttta agacagtttt 360 |
| gtcattactg | gtgggatctg gtcacacaag atagcattaa acgtgacatg gcacataaaa 420 |
| ttgggtaaaa | aattttgttt tttaattacg taatgtaaaa gccaacaaa cactttatgc 480  |
| aagattggaa | tgtatcttca aattcagatt taataaacat gtaaagatcc tctgtatata 540 |
| aaagttgtat | ttaatccctt gtgccccaa aatgctataa aagatcccaa gaatgttatc 600  |
| tatgaaaaga | tagcaatagg gaatggtgaa caaataattt aatttgccaa ttctaaaaaa 660 |
| catggactta | aaccccatga aaacttggtt ccatagtttt aactgtttta tggttccaat 720 |
| acaaaaccag | agtggtttac attccacaat naccaaaatt gcatccaatn ttggggtaat 780 |
| tttnggtatt | tgccatggga tactattcat tttt 814                             |

<210> 59  
 <211> 1215  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (345)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1024)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1098)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1186)  
 <223> n equals a,t,g, or c

|   |      |
|---|------|
| <400> 59  |      |
| agaggaagtc ttttgccaag cctgttctct ggactaacgc catccaggct gggaggggaa   | 60   |
| gagtgtctctg ctacactcgt cccctctctg cctcatcttc cttctcagcc ttggttctctg | 120  |
| atgggaacag aatggagggc ctgagaacat actttctaaa tgcccttgac ccaggaaccg   | 180  |
| attatctata tttgttccca ttttccttca cctgtgacatt ccagcattgt ctgactgtga  | 240  |
| ggtgggcctt tgagagcctc cagggttcctc aaaacaggcc tgagcgatgg gcatcacacc  | 300  |
| ctctgcctac ccacrtgcct gcttacctgc cagataacca agtgnagatg tctgcgagtg   | 360  |
| gctagttttc acattcttac tagtgtttgg ytcacctttg ggcaaaggcc ccctctaggc   | 420  |
| cttgccccac ctccatcaaa cgcagacact gtagtcagac ctcahyaata taggaggcaa   | 480  |
| taatctttta acagtgtttt gcaaacaaac aaaaagagaa aaatcccagc caggggaact   | 540  |
| cgccacctgc ccacgctagt tccatccacg ctcaagaccc gcccttagac caggcaggca   | 600  |
| aaggccccc aacactcgg ccactagtgg ggtcctgagg ccaagaaaga aaccagaccc     | 660  |
| tgtatgacaa gttgggktct ttccagaaca cgacagaaac agggggggcc ccttgtaaat   | 720  |
| gccactccat actccagaag cattattcct tatttgggac agccaagggc agattcacag   | 780  |
| gttattgtag gaataaagac tagtttacaa aggaraaaga gscctggac ttcccmagga    | 840  |
| aaggtcagggt tagggctcct gtacccattc tgttccacca ctgtttgatc tctctggcct  | 900  |
| cccaccagga atgcccgttc ctttttatgg atctgttggg aaccagagag aatcaacaga   | 960  |
| tcaatgacat aggatccgaa gtgcaatgat agtcacttct agtttggcat ttcacaaact   | 1020 |
| ctgnacagca aggtattggg aggttactca atttcaaaag ggccccatgg ccaaatatgt   | 1080 |
| ttaggaaccg ctgtttgnat ttcttttttt ggagacgcat tgtatataat atatgtcaaa   | 1140 |
| ggctttcgga attcctgcag gaaagaaatc agctttgtta aatccnaaaa aaaaaaaaaa   | 1200 |
| aaaaaaatag actcg  | 1215 |

<210> 60  
 <211> 478  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (410)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (476)

<223> n equals a,t,g, or c

<400> 60

|            |             |            |            |             |            |     |
|------------|-------------|------------|------------|-------------|------------|-----|
| atttcttatg | acatgggggt  | ttgaattggt | tggcaaagt  | ttaatttta   | tatccataat | 60  |
| cagtgaagtc | ctgctggctg  | taatcattaa | ttgtgaaatc | taaggagctt  | agttcatggc | 120 |
| tctagaattt | cacagaaaar  | tgygmtatga | tacgagcatt | aagtttattt  | cttctgatct | 180 |
| ttgatgcagc | tttgttcagt  | ttatctgttt | ttgtatttat | tggatcatcta | cttcccatgc | 240 |
| caaaagggac | tggctctacat | agctgcgcta | aacacctgat | caaataccta  | aaagaaaatg | 300 |
| tgttacctct | aatgaattat  | cctgattgta | agttaaaaat | caatatttcc  | ccgtagtgag | 360 |
| gtttgctttt | taaaaagaak  | kcttaaaaaa | aaaaaaaaaa | aaacgagtn   | aagaaaagga | 420 |
| agcaagctca | ggtaagggtc  | acacattggg | ctaaggaagc | tagagcctgt  | ggagangc   | 478 |

<210> 61

<211> 618

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (548)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (560)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (562)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (584)

<223> n equals a,t,g, or c

<400> 61

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| tatgaccttg | ataaccccaa | gttngaaatt | aaccttcant | aaagggaaca | aaagctggag | 60  |
| ttcgcgct   | tcagttcga  | cactagtggg | tcccaaagaa | ttcggcacga | gtcataatga | 120 |
| gctactaggt | aagccttctg | ggactttcag | atattttggg | gaagattgat | ttttgttctt | 180 |
| acatgctgtg | gaccttggc  | catcaaattg | tatggggaag | ctcatccgtc | tgtctgtgat | 240 |

|  |     |
|--|-----|
| gggtcatgtca gtcaggcgctc ttttttagtat ttactgggtg ctcagtactg tgccagatgc | 300 |
| tgctcgggagc cgtgggtggta tggaggagga gtgctccaga ggactctgct gtgtggcagg  | 360 |
| ccagcataaa caagccaagg ggaaaaggca ggcattggaat aaagggggag aataccagtg   | 420 |
| tgtgacttac tgctgactgt gtggattagc ctatcagcag taatcaagca gggcggaggg    | 480 |
| cattatcttt gagccagaag agtgagcact ggsccgaggg tggagcatca agaggggggtg   | 540 |
| taggaccnca aggcttcttn cnggggagac aacgtcaata agcngtcagt agtcaccgac    | 600 |
| agttttggga agcaaggg  | 618 |

<210> 62  
 <211> 751  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (158)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (159)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (202)  
 <223> n equals a,t,g, or c

|  |     |
|--|-----|
| <400> 62   |     |
| tcgacccacg cgtccgagga gctggacttc tgagacagcc attctccttg catagcactg  | 60  |
| tctgtgcta cagctcatag aagtcaacaa ttttcttcaa cactggtagg cagcctctaa   | 120 |
| atggcctga tcaccctcac ctccctgccat tcacaccnnt gtaaaattcc acccctggac  | 180 |
| ctagtgactc acttctaaca angagaatac agcaaaagta acatcgcttc tgaggtagg   | 240 |
| ctacaaggag actacgatgc ctgccttggt cacccttctc ctgctctttc cattgctccc  | 300 |
| tctgatggaa gccagttgcc atgtgatgag gtgcctatg gagaggccca cgtgacaagg   | 360 |
| tattgtaaaa agcctctgac caatagccat ctagaaacgg aggccagtc cagcagcctc   | 420 |
| tgagatgaat cctgccaac tgagcttgga gacagattct ctccctatcc tgccttgga    | 480 |
| tgatcacagc caccaccaac accttcactg cctgggtgaga ggccaagcca gtgaacccaa | 540 |
| ggtaaacctg acagaatcct gaccacaga aactgagata atgtttgtta ttttaagctg   | 600 |
| ctcagtttgt tacagagcaa tagataacta actcaaacac cataaaatcc taatatttta  | 660 |
| ttctatcaca caaaccaggt aataccaagt aaatgccatt actatacaca tatttttgta  | 720 |
| acacaattac atgtgatttt ttaagaaggc t                                 | 751 |

<210> 63  
 <211> 780  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (2)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (4)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (738)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (776)

<223> n equals a,t,g, or c

<400> 63

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| cngncagtc  | cngtccccga | ttcccgggtc | gacccacgcg | tccgggttgg | caactcctga  | 60  |
| ggcctgcatg | ggtgacttca | cattttccta | cctctccttc | taatctcttc | tagagcacct  | 120 |
| gctatcccca | acttctagac | ctgctccaaa | ctagtgacta | ggatagaatt | tgatccccta  | 180 |
| actcactgtc | tgcggtgctc | attgctgcta | acagcattgc | ctgtgctctc | ctctcagggg  | 240 |
| cagcatgcta | acggggcgac | gtcctaatac | aactgggaga | agcctcagtg | gtggaattcc  | 300 |
| aggcactgtg | actgtcaagc | tggcaagggc | caggattggg | ggaatggagc | tggggcttag  | 360 |
| ctgggaggtg | gtctgaagca | gacagggaat | gggagaggag | gatgggaagt | agacagtggc  | 420 |
| tgggtatggc | ctgaggctcc | ctggggcctg | ctcaagctcc | tcctgctcct | tgctgttttc  | 480 |
| tgatgatttg | ggggcttggg | agtccctttg | tcctcatctg | agactgaaat | gtggggatcc  | 540 |
| aggatggcct | tccttcctct | tacccttcct | ccctcagcct | gcaacctcta | tcctggaacc  | 600 |
| tgtcctccct | ttctcccca  | ctatgcactc | gttgtctgct | cctctgcaaa | ggccagccag  | 660 |
| cttgggagca | gcagagaaat | aaacagcatt | tctgatgcc  | aaaaaaaaa  | aaaaaaaaacc | 720 |
| gcgccgaaa  | gcttattncc | ctttaagtaa | ggggttaatt | tttagcttgg | gcactnnggc  | 780 |

<210> 64

<211> 588

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (565)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (566)

<223> n equals a,t,g, or c

<400> 64

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ttccgaatta | atcgactcac | tataggaawt | gccgtcgcca | tgacccgcgg | taaccagcgt | 60  |
| gagctcgccc | gccagaagaa | tatgaaaaag | cagagcgact | cggttaaggg | aaagcgccga | 120 |
| gatgacgggc | tttctgctgc | cgcccgcaag | cagagggact | cggagatcat | gcagcagaag | 180 |
| cagaaaaagg | caaacgagaa | gaaggaggaa | cccaagtagc | tttgtggctt | cgtgtccaac | 240 |
| cctcttgccc | ttcgctgtg  | tgcctggagc | cagtccacc  | acgctcgctt | ttcctcctgt | 300 |
| agtgtcaca  | ggtcccagca | ccgatggcat | tccttttgcc | ctgagtctgc | agcgggtccc | 360 |
| ttttgtgctt | ccttcccctc | aggtagcctc | tctccccctg | ggccactccc | gggggtgagg | 420 |
| gggttaccct | ttcccagtgt | tttttattcc | tgtggggctc | accccaaagt | attaaaagta | 480 |
| gctttgtaat | tccaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 540 |

aaaaaaaaa aaaaaaaaaa aaaanncggg ggggggcccc ccccccc

588

<210> 65  
 <211> 945  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (13)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (15)  
 <223> n equals a,t,g, or c

<400> 65  
 naatacgc atnanagggc gattgggtac gggccccccc tcgagttttt tttttttttt 60  
 tttggcaagt gagaagatgc agataggcaa aaagraaaaa aaagagatca cacagagatt 120  
 cactgttaac ctttgggtgta taataaaatc agacactttc ctttgcatta tgtcacatag 180  
 aaatgtacaa ataaagtgt catatatata cacatatatg tatacactgt tttgcaactc 240  
 gttattttca ctttgcaata tacaatgagc atttttccat gcaaatgaat gagacctctt 300  
 attaaatgaa taagattggg tcaaaagatg agatgttgac aagagtcata tgtaaatctc 360  
 agcaacatcg aatgactgga gtaaaacgat agcaaatatt tatcaagaaa gtgcagacaa 420  
 acagaaagca gtggcaacat taataacaga aaataattga attgtcagag aaattaatta 480  
 aatgggataa ggacggtccc gagaatgcct atgggttagaa tgcagagccc taaatttctt 540  
 tctyagacc cttatctctt ccaaacacct ttccatctca tctccctccc ttgtcatttc 600  
 ttcatcttta aaatgcctat agtctatgtc ctctttaaat tcttcgagag actgaagcag 660  
 cctctgtcta aaattccctt ctgtttgctg gcgttcaa tctccatacg ggcgtttttc 720  
 ctccctcttt ggcacgctgc actttggctt tccctcgttt tctttgcagg gtttttgcatt 780  
 gatgttggtt ttgtttcctg cttaactctg tgcggggtag tttcctgctc cttttcttcc 840  
 ccagatgtc tgtgaacaca gatcctggga cctcttcctt cccttggcca caagcacgca 900  
 cggcacgctt gtctgcaggg cagtaaggag ctggtacctc gtgcc 945

<210> 66  
 <211> 1866  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (262)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (674)  
 <223> n equals a,t,g, or c

<400> 66

|            |             |            |             |             |             |      |
|------------|-------------|------------|-------------|-------------|-------------|------|
| accacgcgt  | ccggtcctct  | tcttcagcac | atgccaaagc  | tgttcctcac  | ggcctgtgag  | 60   |
| acaagagcat | cttggatgta  | ggacaatgga | agagttagat  | gccttattgg  | aggaactgga  | 120  |
| acgctccacc | cttcaggaca  | gtgatgaata | ttccaaccca  | gctcctcttc  | ccctggatca  | 180  |
| gcattccaga | aaggagacta  | accttgatga | gacttcggag  | atcctttcta  | ttcaggataa  | 240  |
| cacaagtccc | ttgccggcgc  | antcgtgtat | actaccaata  | tccaggagct  | caatgtctac  | 300  |
| agtgaagccc | aagagccaaa  | ggaatcacca | ccaccttcta  | aaacgtcagc  | agctgctcag  | 360  |
| ttggatgagc | tcatggctca  | cctgactgag | atgcaggcca  | aggttgcagt  | gagagcagat  | 420  |
| gctggcaaga | agcacttacc  | agacaagcag | gatcacaaag  | cctccctgga  | ctcaatgctt  | 480  |
| gggggtctsg | agcaggaatt  | gcaggacctt | ggcattgcca  | cagtgcacca  | gggccattgt  | 540  |
| gcatcctgcc | agaaaaccgat | tgctgggaag | gtgatccatg  | ctctagggca  | atcatggcat  | 600  |
| cctgagcatt | ttgtctgtac  | tcattgcaaa | gaagagattg  | gctccagtcc  | cttctttgag  | 660  |
| cggagtggct | tggntactctg | ccccaacgac | taccaccaac  | ttttttctcc  | acgctgtgct  | 720  |
| tactgcgctg | ctcccatact  | ggataaagtg | ctgacagcaa  | tgaaccagac  | ctggcaccca  | 780  |
| gagcacttct | tctgctctca  | ctgcggagag | gtgtttgggtg | cagaaggctt  | tcatgagaag  | 840  |
| gacaagaagc | catattgccg  | aaaggatttc | ttagccatgt  | tctcacccaa  | gtgtgggtggc | 900  |
| tgcaatcgcc | cagtgttgga  | aaactacctt | tcagccatgg  | acactgtctg  | gcaccagag   | 960  |
| tgctttgttt | gtggggactg  | cttcaccagt | ttttctactg  | gctccttctt  | tgaactggat  | 1020 |
| ggagctccat | tctgtgagct  | ccattaccat | caccgccggg  | gaacgctctg  | ccatgggtgt  | 1080 |
| gggcagccca | tcactggccg  | ttgtatcagt | gccatggggt  | acaagttcca  | tcctgagcac  | 1140 |
| tttgtgtgtg | ctttctgcct  | gacacagttg | tcgaagggca  | ttttcaggga  | gcagaatgac  | 1200 |
| aagacctatt | gtcaaccttg  | cttcaataag | ctcttcccac  | tgtaatgcca  | actgatccat  | 1260 |
| agcctcttca | gattccttat  | aaaattttaa | ccaagagagg  | agaggaaagg  | gtaaattttc  | 1320 |
| tgttactgac | cttctgcctt  | atagtcttat | agaaaaagga  | aagggtgatga | gcaaataaag  | 1380 |
| gaacttctag | actttacatg  | actaggctga | taatcttatt  | ttttaggtct  | ctatacagtt  | 1440 |
| aattctataa | attctctttc  | tccctctctt | ctccaatcaa  | gcacttggag  | ttagatctag  | 1500 |
| gtccttctat | ctcgtccctc  | tacagatgta | ttttccactt  | gcataattca  | tgccaacact  | 1560 |
| ggttttctta | ggttttctcca | ttttcacctc | tagtgatggc  | cctactcata  | tcttctctaa  | 1620 |
| tttggctctg | atacttggtt  | cttttcacgt | tttcccattt  | ccctgtggct  | cactgtctta  | 1680 |
| caatcactgc | tgtggaatca  | tgataccact | tttagctctt  | tgcactcttc  | ttcagtgtat  | 1740 |
| ttttgttttt | caagaggaag  | tagattttta | ctggacaact  | ttgagtactg  | acatcattga  | 1800 |
| taaataaact | ggcttgtggt  | ttcaataaaa | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | 1860 |
| aaaaaa     |             |            |             |             |             | 1866 |

&lt;210&gt; 67

&lt;211&gt; 1152

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (668)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (745)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1015)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1088)

&lt;223&gt; n equals a,t,g, or c



<220>  
 <221> SITE  
 <222> (1110)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1113)  
 <223> n equals a,t,g, or c

<400> 67  
 ctcaaggatg taaaggctct gcagatttcg ggaggcctgt ctcccagcac ctgatgggac 60  
 actttttgcc ccactgtaaa ttctgggtgt atcctccact gtatgctgtc accccaaggg 120  
 caagcactgc atctgcttag tgaaggattt attgttcgga agatacattt tccccttkag 180  
 cagagagtgg cgtatcctgg cagtcttcgg tgagccagtt gtaccaggat tatgaaatgc 240  
 agatgtttac tgtgtcattg ttgctgtcat tgctactgag gactactgac cagaatcatc 300  
 tgcaactytt agttggcaga gaggaccact atggcgggta gctcttttct ttcctgccat 360  
 tgtgggggatg attccaggcc aaagatgatg garaagtatg gaaatcatct gaaagggtga 420  
 agcttggcac gtgaagccat tcatgacttt gtaaggcagt tttgctgaag gccagttctg 480  
 ccctgggagg gacggaggtg aatcctcctg agtacctgtg gttttcttac ttcctgctga 540  
 atttacctaa gtgcctgttg tttgcttgct gtggaggcct tctggtattt catttcaggt 600  
 gcagatgcct tcactttccc accraaaaaa ccccmaccaa acctaagacc ttactgcaac 660  
 taagtytncc aagtactttt taacccaatg ggatgaacag cctgtgggtct gctcagatca 720  
 ccctgagtgc gtgtgagaag gcmtnnggctt tgccaggaaa tccagggaagg cagggccggg 780  
 ctgtgttgga agctggccta gctgggtggg cagccttatt tcaattaaaa gggcattgac 840  
 tgggagcagc agtcctggag tttgttgcac ttcctattgc cctcaaatg agaaaccagg 900  
 aaaatagcag attggagcct tcgagaaggc agtaaattggc tgtttttatt gacaaaagga 960  
 aaacatttta ctgccatctc actgatggca tctcactgac ttaaaatgaa ggcangttgt 1020  
 agtaaaaaaa aaagtctaca tttttccacc gccacgttct tatatcctgt ttgtcagcca 1080  
 ctgctcanaa gggcatgttg tcttgcggan tanaggcgct ctccctccct cgttttccct 1140  
 ataggttggg tg 1152

<210> 68  
 <211> 2483  
 <212> DNA  
 <213> Homo sapiens

<400> 68  
 agcaggcggg gcgctggggg cgggagcagc gcgkagcccg gctcggccac accgatcgcc 60  
 cgccgccatg ggctcctcgc aaagcgtcga gatcccgggc gggggcaccg agggctacca 120  
 cgttctgcgg gtacaagaaa attccccagg acacagagct ggtttgagc ctttctttga 180  
 ttttattgtt tctattaatg gttcaagatt aaataaagac aatgacactc ttaaggatct 240  
 gctgaaasca aacggtgaaa agcctgtaaa gatgcttacc tatagcagca aaacattgga 300  
 actgcgagag acctcagtca caccaagtaa cctgtggggc ggccagggtt tattgggagt 360  
 gagcattcgt ttctgcagct ttgatggggc aaatgaaaaat gtttgcatg tgctggagggt 420  
 ggaatcaaat tctcctgcag cactggcagg tcttagacca cacagtgatt atataattgg 480  
 agcagatata gtcattgaat agtctgaaga tctattcagc cttatcgaaa cacatgaagc 540  
 aaaaccattg aaactgtatg tgtacaacac agacactgat aactgtcgag aagtgattat 600  
 tacaccaaat tctgcattgg gtggagaagg cagcctagga tgtggcattg gatatgggta 660  
 tttgcattga atacctacac gccatttga ggaaggaaag aaaatttctc ttccaggaca 720  
 aatggctggt acacctatta cacctcttaa agatgggttt acagagggtc agctgtcctc 780  
 agttaatccc ccgtctttgt caccaccagg aactacagga attgaacaga gtctgactgg 840  
 actttctatt agctcaactc caccagctgt cagtagtggt ctacgtacag gtgtaccaac 900  
 agtaccgtta ttgccaccac aagtaaacca gtccctcact tctgtgccac caatgaatcc 960  
 agctactaca ttaccaggtc tgatgccttt accagcagga ctgcccacc tcccacact 1020  
 caacctcaac ctcccagcac cacacatcat gccagggggt ggcttaccag aacttgtaaa 1080

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cccagggtctg | ccacctcttc  | cttccatgcc  | tccccgaaac  | ttacctggca  | ttgcacctct  | 1140 |
| ccccctgcc   | tccgagttcc  | tcccgtcatt  | ccccttggtt  | ccagagagct  | cttctgcage  | 1200 |
| aagctcagga  | gagctgctgt  | cttcccctccc | gcccaccagc  | aacgcaccct  | ctgaccctgc  | 1260 |
| cacaactact  | gcaaaggcag  | acgctgcctc  | ctcactcact  | gtggatgtga  | cgccccccac  | 1320 |
| tgccaaggcc  | cccaccaccg  | ttgaggacag  | agtcggcgac  | tccaccccag  | tcagcgagaa  | 1380 |
| gcctgtttct  | gcggctgtgg  | atgccaatgc  | ttctgagtca  | ccttaacttt  | gaaccattct  | 1440 |
| ttggaattgg  | cgtggtatat  | ttaaccacgg  | gagcgtgtct  | ggaaacgcaa  | actatcatta  | 1500 |
| atttcatact  | agtttgtacc  | gtatctgtag  | gcacctctga  | aataattcca  | aggggaaaac  | 1560 |
| taaacgagga  | cgtgggttgt  | atcctgccag  | gttgagtggg  | gctcacacgc  | taggggtgaga | 1620 |
| tgtcagaaag  | cgcttgattt  | ttaaacaacc  | aaaaagaatt  | gtaagggtgg  | cttgctgcc   | 1680 |
| ggcttgcact  | gccgttcctg  | gggggtgtga  | tcttcgggaa  | aggtggtggc  | ggggcgctcca | 1740 |
| ctagggtttcc | tgtcccctgc  | tgctccttcc  | gtaagaaaat  | gaaatattct  | atgcctaata  | 1800 |
| ctcacacgca  | acatttcttg  | tactttgtaa  | gtcgtttgcg  | agaatgcaga  | ccacctcact  | 1860 |
| aaactgtaaa  | cgttaaagag  | atttttactt  | ttggtctccg  | tgagtgcgat  | ctctactaag  | 1920 |
| gtttacacag  | gaattccacc  | tgaagacttg  | tgttaaagtt  | ctacagcgcg  | cactgttaac  | 1980 |
| tgaacgtctt  | tttcttcagc  | ctatacgcgg  | atccttgttt  | tgagctctca  | gaatcactca  | 2040 |
| gacaacattt  | tgttaactgt  | gctgttgctt  | tctacatata  | ccttataaag  | tgacatttca  | 2100 |
| aaagaaataa  | ggtgcccacag | ttttaaacca  | gaagggtggc  | ctctgtggct  | ccttgtagta  | 2160 |
| ttatagctat  | actgggaaaag | catagatata  | gcaataaagt  | acagtaattt  | tacttttttt  | 2220 |
| cttgtgttac  | atctaaatta  | caacccttaa  | ttgccacgtg  | tgcaacttact | actctccagt  | 2280 |
| atgtcttatt  | actctccagt  | atgtcacgca  | tctttaactt  | ttcacgtcct  | atgtttgctt  | 2340 |
| tctcccatct  | ttaagagatg  | gtaagttaac  | tggaattgat  | ttactgaatg  | aaattaaatg  | 2400 |
| cagatatccc  | tgtttttgaa  | ataaaaaaaaa | aaaaaaaaaaa | aaaaaaaaaaa | aaaaaaaaaaa | 2460 |
| aaaaaaaaaa  | aaaaaaaaaa  | aaa         |             |             |             | 2483 |

&lt;210&gt; 69

&lt;211&gt; 536

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 69

|            |            |             |            |            |            |     |
|------------|------------|-------------|------------|------------|------------|-----|
| gagaaatgga | gctttgttag | ataaaaattt  | tttcaacgca | aacagtcatt | ttccagtga  | 60  |
| aggagagcgt | atccgcccga | ggatggactt  | agatcgtgta | aaagctgagg | ccaccgagga | 120 |
| tataacctcc | ggggctcctt | gcctcctttt  | ccttagactc | cctccaaact | cgtgtatctt | 180 |
| tccttcagca | gtactgggct | ccacgcgaac  | ctagtccctt | gtctttaccc | tattaccttt | 240 |
| cataacatcc | tagttgaaaa | gtarttattc  | aaccgcgttt | gaaaatgaga | acaggttcac | 300 |
| agargctagg | ttacttgcca | aggtcgttca  | attagtaacc | agtaacgcca | ggactgccag | 360 |
| tttcttgctt | ccgaattctc | atggttagctt | tcaccargct | ccccgtcmaa | tgctaacgtc | 420 |
| aactactgaa | ctagattagc | aaaaaggctc  | tttaacagaa | ttcctgggtt | tcagagagag | 480 |
| tttctttcat | gaagcgcccc | atttctacag  | aggaaaataa | actccaagca | gccagt     | 536 |

&lt;210&gt; 70

&lt;211&gt; 574

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 70

|            |            |             |            |            |            |     |
|------------|------------|-------------|------------|------------|------------|-----|
| ggggggcgaa | ttcccctggc | acgaggctga  | cgcattgcga | tagctaaccg | caccgcgttc | 60  |
| agctcgcctt | tcttgccag  | aggcgccggt  | tggactcacg | ggcggggcat | gatgggtgtg | 120 |
| ggtacgggca | cctcgctggc | gctctcctcc  | ctcctgtccc | tgctgctctt | tgctgggatg | 180 |
| cagatgtaca | gccgtcagct | ggcctccacc  | gagtggctca | ccatccaggg | cggcctgctt | 240 |
| ggttcgggtc | tcttcgtgtt | ctcgcctcact | gccttcaata | atctggagaa | tcttgtcttt | 300 |
| ggcaaaagat | tccaagcaaa | gatcttccct  | gagattctcc | tgtgcctcct | gttggctctc | 360 |
| tttgcatctg | gcctcatcca | ccgagtctgt  | gtcaccacct | gcttcatctt | ctccatgggt | 420 |
| ggtctgtact | acatcaacaa | gatctcctcc  | accctgtacc | aggcagcagc | tccagtcctc | 480 |
| acaccagcca | aggtcacagg | caagagcaag  | aagagaaact | gacctgaat  | gttcaataaa | 540 |

gttgattctt tgtaaaaaaa aaaaaaaaaa aaaa

574

<210> 71  
 <211> 932  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (884)  
 <223> n equals a,t,g, or c

<400> 71  
 tcacatata caaagttttt cgtcacactg cagggttgaa accagaagtt agttgctttg 60  
 agaacataag gtcttgtgca agaggagccc tcgctcttct gttccttctc ggcaccacct 120  
 ggatcttttg ggttctccat gttgtgcacg catcagtggg tacagcttac ctcttcacag 180  
 tcagcaatgc tttccagggg atgttcattt ttttattcct gtgtgtttta tctagaaaga 240  
 ttcaagaaga atattacaga ttgttcaaaa atgtcccctg ttgttttgga tgtttaagggt 300  
 aaacatagag aatgggtggat aattacaact gcacaaaaat aaaaattcca agctgtggat 360  
 gaccaatgta taaaaatgac tcatcaaatt atccaattat taactactag acaaaaagta 420  
 ttttaaatca gtttttctgt ttatgctata ggaactgtag ataataagggt aaaattatgt 480  
 atcatataga tatactatgt ttttctatgt gaaatagttc tgtcaaaaat agtattgcag 540  
 atatttggaa agtaattggg ttctcaggag tgatatcact gcacccaagg aaagattttc 600  
 tttctaacac gagaagtata tgaatgtcct gaaggaaacc actggcttga tatttctgtg 660  
 actcgtgttg cctttgaaac tagtccccta ccacctcggg aatgagctcc attacagaaa 720  
 gtggaacata agagaatgaa ggggcagaat atcaaacagt gaaaagggaa tgataagatg 780  
 tattttgaat gaactgtttt ttctgtagac tagctgagaa attgttgaca taaaataaag 840  
 aattgaagaa acacatttta ccatttaaaa aaaaaaaaaa actngagggg ggcccgggtac 900  
 ccaaatcgcc gcatagtgat cgtaaacat ct 932

<210> 72  
 <211> 996  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (584)  
 <223> n equals a,t,g, or c

<400> 72  
 cgcttgccac catgaggacg cctgggcctc tgcctgtgct gctgctgctc ctggcgggag 60  
 cccccgccgc ggggcccact ccccgacct gctactcccg catgcgggcc ctgagccagg 120  
 agatcaccgc cgacttcaac ctctgcagg tctcggagcc ctcgagcca tgtgtgagat 180  
 acctgccag gctgtacctg gacatacaca attactgtgt gctggacaag ctgcgggact 240  
 ttgtggcctc gccccgtgt tggaaagtgg cccaggtaga ttccttgaag gacaaaagc 300  
 ggaagctgta caccatcatg aactcgttct gcaggagaga tttggtatc ctgttgatg 360  
 actgcaatgc cttggaatac ccaatcccag tgactacggg cctgccagat cgtcagcgt 420  
 aagggaactg agaccagaga aagaacccaa gagaactaaa gttatgtcag ctaccagac 480  
 ttaatgggca agagccatga ccctcacagg tcttgtgtta gttgtatctg aaactgttat 540  
 gtatctctct accttctgga aaacagggct ggtattccta cccnggaacc tcctttgagc 600  
 atagagttag caaccatgct tctcattccc ttgactcatg tcttgccagg atgggttagat 660  
 acacagcatg ttgatttggt cacctaaaaa gaagaaaagg actaacaagc ttcactttta 720  
 tgaacaacta ttttgagaac atgcacaata gtatgttttt attactgggt taatggagta 780  
 atggtacttt tattctttct tgatagaaac ctgcttacat ttaaccaagc ttctattatg 840  
 cctttttcta acacagactt tcttcaactgt ctttcattta aaaagaaatt aatgctctta 900

agatatatat tttaggtagt gctgacagga cccactcttt cattgaaagg tgatgaaaat 960  
 caaataaaga atctcttcac atgaraaaaa aaaaaa 996

<210> 73  
 <211> 785  
 <212> DNA  
 <213> Homo sapiens

<400> 73  
 ggacagagg gctttgcgta cacaatagct gctaggagta cccaaagcct gartacarcc 60  
 tgctggtgtc atggccacgt gtgagcaggc cagcgtcama cggctcgctg tgaccgcgtcc 120  
 cgragactga aatgggcctg ggtcttctcc tkgtcctgtg atwaaagtcc tctcttgaaa 180  
 gtggagagca aaggcacaca gaggtgcgag ctcacaagaa ttctctccgg tgactgggta 240  
 atcaatgtta ctgctgtttc ctttgcagga aagaccacag caagattctt tcattcgtct 300  
 cctcctagcc tgggggacca ggctcgaact gaccctggac atcaaaggag ggattatgtg 360  
 gctgctaaag ccacgcggcc acagccctgt tcacrtcttg gtgcttctct tctccagagg 420  
 ctggtcccag ccaggcacac acaaaaggca gattctctga aacscagcct ccctccctgg 480  
 aggtgcctc ctgccctgga tctggagtgg agctgctctg agattttgag ttcttctgca 540  
 gagatgatta aatatatcca agagacattg gaaaacctgc tgaacatttt acattggtct 600  
 gctcagcaca tggctggatg cggatatttc tataattcca gaaagtcaca cagctcctct 660  
 gtatgagacc agtgggcgcc atttaaaaga acaggatgag aatctaagat atattattaa 720  
 taaatgtaat ggattttttt tttgtaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780  
 aaaaa 785

<210> 74  
 <211> 1069  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (20)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (92)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (886)  
 <223> n equals a,t,g, or c

<400> 74  
 tcctcaccat tcccctaggn caggctccctg caggctccac acttctccca ggtccctaaa 60  
 cttgggtcgg tcctttccct ggagtagctg gntcctccag tcgagggtccc tgttcagtcg 120  
 gttcttaggc tctgcacat gaaggtgtgt gcctgtgggtg tgtgggctgc tctaggagca 180  
 gatacaggct ggtatagagg atgcagaaag gtagggcagt atgtttaagt ccagacttgg 240  
 cacatggcta gggatactgc tcaactagctg tggaggctct caggagtgga gagaatgagt 300  
 aggagggcag aagcttccat ttttgtcctt cctaagaccc tgttatttgt gtatttctct 360  
 gcctttccga gtctgcagt gggctgccct gtaccctgaa cctcatgagc ctctaaggga 420  
 aaggaggpac aattaggacg tggcaatgag acctggcagg gcagartaca agcccagcac 480  
 cagtgtccca gccttactgg gtccttaccg tgggccaaac agggagggtc gatacctct 540  
 tgctcttctc agatgccac ctcctacaat ctcagccac aagtcctctc caccctaggg 600  
 ggcttgctgc atggcaataa ctcataatct gatttgagg tttgcccttt acaggggcag 660

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| attttctgct | cagttcaaca | atgaaatgaa | gaggaactcc | ctctttctac | agctcacttc | 720  |
| tatcagaggg | ccaggtgcct | cagagccaca | ttgagttgct | ttttctggga | tgaggaagta | 780  |
| gggttaaact | ccccagtttc | ctgagggagg | ctcctgacag | gtgccctttg | tcagacccta | 840  |
| ccacagcctg | gataggcagc | cacattggtc | ctcgcccttg | ctcggnactc | cgtggtggtc | 900  |
| ctgcccttct | ccctgcatgc | ctgtgggtct | gctctggtgt | gtgaaggctc | gtgggttaac | 960  |
| tgtgtgccta | ctgaacctgg | caaataaaca | tcaccctgca | aagccaaaaa | aaaaaaaaaa | 1020 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa |            | 1069 |

&lt;210&gt; 75

&lt;211&gt; 831

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

|             |             |            |            |            |            |     |
|-------------|-------------|------------|------------|------------|------------|-----|
| ggacattaga  | tcactgtgga  | cctaaaacaa | acaaacaact | ataaggaaaa | tggcattaga | 60  |
| aatggtctgg  | ggatcagttt  | atcactgcag | ttgttacatc | accccatggg | ctaaaataca | 120 |
| gagctttagt  | ctgtctctgt  | ttcagttcat | tttacaggag | gtgaacatca | cacttccaga | 180 |
| aaactctgtc  | tggtatgaaa  | ggtataaatt | tgatattcct | gtctttcact | tgaatggcca | 240 |
| gtttctgatg  | atgcatcgag  | taaacacctc | aaaacttgaa | aaacagctcc | tgaaacttga | 300 |
| gcagcaaagt  | actggargct  | gactgatgcc | ctcatgattt | tccaccctct | cttcccataa | 360 |
| agcatcttcc  | taaggaaatg  | amcatggcct | gatactcatt | ttgtcacttg | tacagagccc | 420 |
| taaggatggt  | ctgaattcag  | tggtgccaaa | taaatgttga | cattcccctt | ttggttgatg | 480 |
| gaagtatcag  | tgtgggaaact | gtttgcttaa | tggcatttta | taaaataaka | akakcatatt | 540 |
| agcagggagg  | gagatgatgg  | agggagggag | aagtccattt | gtcttattta | tcctttttgt | 600 |
| attaatagag  | aagcacttca  | cagtcactgg | caatgccatt | tataggaaga | aggttctgca | 660 |
| ttcctgctgc  | tcccggaggg  | cttaactttt | taatgaaaga | ataaatgctc | ttccactcag | 720 |
| tagataaaagt | gaaatgtgaa  | ttgttaataa | ctgtgcacgg | tcaataaagc | gatgttttaa | 780 |
| ggaatacaaa  | aaaaaaaaaa  | aaaaaaaaaa | aaaaaaaaaa | aaaaaactcg | a          | 831 |

&lt;210&gt; 76

&lt;211&gt; 590

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (76)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 76

|            |            |             |            |            |            |     |
|------------|------------|-------------|------------|------------|------------|-----|
| tatatataga | cngttaatag | tcgtgantgn  | tgtgnacgaa | cattaacgga | agtagcatgt | 60  |
| agccagtcga | ataacntata | aggacaaagt  | ggagtccacg | cgtgcggccg | tctagactag | 120 |
| tggatccccc | ggctgcagga | ttcggcacga  | gctgccaggt | gaggagcaga | gagactgttc | 180 |
| ccttgggtgg | agaggtgtgg | gcatgagagc  | cacccattgc | caagcagcaa | gaatgttcgt | 240 |
| gcttttttcc | cttccaaaat | atgcagggct  | caggctccca | attccggggc | tgtctgcttt | 300 |
| gcttgtgttt | ctcctgtccc | tggtctcccg  | gagggcccg  | gtggaactca | cgacagggag | 360 |
| ggagacgctt | cccaaaaacc | tgacagggcta | tttcccagaa | tttggttttc | aagtacaaaa | 420 |
| ctttttgtcc | tgtaagatat | atgcagcctc  | acagaagcag | cctctgcctc | cactttacca | 480 |
| gctacgtttt | tatcttaagc | acatggggct  | cccttagaac | ttactccact | gatttaaaaa | 540 |
| aaaaaaaaaa | aaactcgagg | ggggggcccg  | taccattcgc | ccctaaaagt |            | 590 |

&lt;210&gt; 77

&lt;211&gt; 1274

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

|             |            |            |            |            |             |      |
|-------------|------------|------------|------------|------------|-------------|------|
| gagccaccac  | acctggcctg | gaaggaacct | cttaaaatca | gtttacgtct | tgtattttgt  | 60   |
| tctgtgatgg  | aggacactgg | agagagtgc  | tattccagtc | aatcatgtcg | agtcactgga  | 120  |
| ctctgaaaaat | cctattggtt | octttatttt | atttgagttt | agagttccct | tctggggttg  | 180  |
| tattatgtct  | ggcaaatgac | ctgggttatc | acttttcctc | cagggttaga | tcatagatct  | 240  |
| tggaactcc   | ttagagagca | ttttgctcct | accaaggatc | agatactgga | gccccacata  | 300  |
| atagatttca  | tttactcta  | gcctacatag | agctttctgt | tgctgtctct | tgccatgcac  | 360  |
| ttgtgcggtg  | attacacact | tgacagtacc | aggagacaaa | tgacttacag | atccccgac   | 420  |
| atgcctcttc  | cccttgcaa  | gctcagttgc | cctgatagta | gcatgtttct | gtttctgatg  | 480  |
| tacctttttt  | ctcttcttct | ttgcatcagc | caattcccag | aatttcccca | ggcaatttgt  | 540  |
| agaggacctt  | tttgggtcc  | tatatgagcc | atgtcctcaa | agctttttaa | cctccttgct  | 600  |
| ctcctacaat  | attcagtaca | tgaccactgt | catcctagaa | ggcttctgaa | aagaggggca  | 660  |
| agagccactc  | tgccgccaca | agggtggggg | ccatcttctc | tccgaggttg | tgaaagtttt  | 720  |
| caaattgtac  | taataggatg | gggccctgac | ttggctgtgg | gctttgggag | gggtaagctg  | 780  |
| ctttctagat  | ctctcccagt | gaggcatgga | ggtgtttctg | aattttgtct | acctcacagg  | 840  |
| gatgttgatg  | ggcttgaaaa | ggtcaaaaaa | tgatggcccc | ttgagctctt | tgtaagaaag  | 900  |
| gtagatgaaa  | tatcggatgt | aatctgaaaa | aaagataaaa | tgtgacttcc | cctgctctgt  | 960  |
| gcagcagtcg  | ggctggatgc | tctgtggcct | ttcttgggtc | ctcatgccac | cccacagctc  | 1020 |
| ccaggaacct  | tgaagccaat | ctgggggact | ttcagatggt | tgacaaagag | gtaccaggca  | 1080 |
| aacttcctgc  | tacacatgcc | ctgaatgaat | tgctaaattt | caaaggaaat | ggacctgtct  | 1140 |
| tttaaggatg  | tacaaaagta | tgtctgcac  | gatgtctgta | ctgtaaattt | ctaattttatc | 1200 |
| actgtacaaa  | gaaaacccct | tgctatttaa | ttttgtatta | aaggaaaata | aagttttgtt  | 1260 |
| tgttaaaaaa  | aaaa       |            |            |            |             | 1274 |

&lt;210&gt; 78

&lt;211&gt; 1133

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| aggatttttc | cttgttcaac | caaaatctga | gcattctttc | tatgttgaaa | acactgaaaa | 60  |
| actaatttwa | gttaatgaac | tagaaagaat | attgattttw | aagaaacaga | aaaatactac | 120 |
| ttatttttct | tctcaataaa | cgtttctttc | aaaaacttct | ggctgaagta | taacatgctg | 180 |
| gtagttaaca | taaactcttg | ctttctcttg | ttctttatct | ttctttgtta | tttagatgct | 240 |
| tgtataaatg | tcttttggtt | ttattaagtg | cctaattgac | agagcttaat | ttgaagaagt | 300 |
| gccctaattt | attgaccact | taagaattgc | ctttattggg | gtattttatt | tgttcctgcg | 360 |

|            |             |            |             |            |            |      |
|------------|-------------|------------|-------------|------------|------------|------|
| tctttttgat | gttggttcagt | ctactcatcc | ctgtgagtat  | gtgtggggga | cagctgatag | 420  |
| aagggaggag | agtgtgtcta  | tgctcaggat | tgcccttttag | ccactcagcc | agagatccac | 480  |
| agggagcaac | aaggacagtt  | tcacatgctt | agactttctt  | ggaagaaaca | gtgaggagga | 540  |
| gtaagtcgtg | agtagtgtca  | agctggatgt | agaattgtcc  | taaggcagtt | gacccacct  | 600  |
| tccaacatgt | tttcaactta  | tttggccctc | cctacatttg  | ggtaggttc  | catttggtt  | 660  |
| tgcagcaata | atgactttat  | ttctctcttg | gtcaggattt  | ggcacataaa | atccttttat | 720  |
| tatagaacta | gctatttttag | ttacatagta | atgtaactaa  | tggagagatt | tatagagaat | 780  |
| tttgkttttg | ctgtcatata  | tgtccatttt | ggagacagat  | atgatagaac | tagaaattaa | 840  |
| gttgcatctc | tgcaagtgcc  | atttgaatga | acttcaagta  | tcttcttaat | tattaaattt | 900  |
| tctgatgaag | gcattgtaac  | aaatatatag | tattattaaa  | tctaattaat | atttggaat  | 960  |
| attaataaat | aggtattttta | tttactgtaa | aaagtcaaac  | ttcattatgt | agataaatct | 1020 |
| tattcttttc | attctttccc  | ctgtttacat | cctttttaca  | aagcttagtc | accaattaaa | 1080 |
| gctttcttat | caaaaaaaaa  | aaaaaaaaaa | actcgagact  | agttctctct | cct        | 1133 |

&lt;210&gt; 79

&lt;211&gt; 661

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

|            |            |             |            |             |            |     |
|------------|------------|-------------|------------|-------------|------------|-----|
| gaattcggca | cgaggggaaa | aggatgctga  | acgagagcag | aaagcctctt  | tcctttgctt | 60  |
| cacgcctttc | cagtctttat | tttaaaactcg | ggttcccttt | ctgtgggtcgc | agcaaccttt | 120 |
| actccacctg | cactgctgct | cctgggggct  | ccccaggcct | ccctctgcct  | ttctaccacg | 180 |
| tggtgacgg  | gatgcctgtc | ttgcctggac  | gcaccactgc | tctcctgtcc  | ctcaccttgg | 240 |
| cttttgctgt | gccctgctct | gggggtgaag  | ctggcccatg | tgtcccccg   | agtcattggc | 300 |
| gctcctcctg | ggaggcctct | gtgtgcgtca  | cgtcttccac | acctgggggc  | agctggcgag | 360 |
| cccgtgctct | gttcccctcg | gctgcttggc  | acagagytgc | agcctgggag  | tctccgtgga | 420 |
| ccagactgg  | ggattttgcc | agggggcgga  | tgggaggagc | aggtgctttg  | cctggcggtc | 480 |
| gtgtctgcat | ttctggacgc | cccagagcac  | agaagttgcc | ggcactttga  | ggtcttcttc | 540 |
| ggcatgtgcc | agattacatg | agtgacggct  | gggaatatgt | tttctttttt  | gtaatggagg | 600 |
| cgtgtttcac | atatagtaaa | gctcaccaaa  | aagtaaaaaa | aaaaaaaaaa  | aaaaaactcg | 660 |
| a          |            |             |            |             |            | 661 |

&lt;210&gt; 80

&lt;211&gt; 1378

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

|            |             |             |            |             |            |      |
|------------|-------------|-------------|------------|-------------|------------|------|
| agacgtgaaa | catgtgaaca  | ctcaagtga   | gcaaaagcct | tccatgatta  | cccttttatg | 60   |
| tcacctcggt | accctggagg  | tccaaggccc  | ccattgagga | tacctaataca | ggcacttgga | 120  |
| ggtgtcccag | gaagtcagcc  | attactcccc  | agtggaatgg | atccaactcg  | acaacaagga | 180  |
| catccaaata | tgggtgggccc | aatgcagaga  | atgactcctc | caagaggaat  | ggtgccctta | 240  |
| ggaccacaga | actatggagg  | tgcaatgaga  | ccccactga  | atgcttttagg | tggccctgga | 300  |
| atgcctggaa | tgaacatggg  | tccaggtggg  | ggtagacctt | ggccaaaccc  | aacaaatgcc | 360  |
| aattcaatac | catactcctc  | agcatctcct  | gggaattatg | taggtcctcc  | aggaggtgga | 420  |
| gggccaccag | gaacacccat  | catgcctagt  | ccagcagatt | caaccaactc  | tggtgataac | 480  |
| atgtatactt | taatgaatgc  | agtacctcct  | ggacctaaac | gacctaat    | tccaatgggy | 540  |
| ctggggtcag | atggtcccat  | gggtggatta  | ggaggaaatg | agtcacatca  | catgaatggc | 600  |
| tctttaggct | caggagatat  | ggacagtatt  | tccaagaatt | ctcccaataa  | tatgagcctg | 660  |
| agtaatcaac | cgggcactcc  | aagggatgat  | ggcgaaatgg | ggggaaat    | cttaaatcct | 720  |
| tttcagagt  | agagttactc  | ccctagcatg  | acaatgagcg | tgtgatccat  | taccaagtct | 780  |
| cctcatgaaa | accacagtga  | gtcagccctt  | cacagaacta | ctacggaaga  | aaattattca | 840  |
| tcacagtgt  | cagttaaaca  | aagggaatctc | agtcacacca | aaccaacctt  | tttatttctc | 900  |
| gctctctccc | ctcttttgtg  | aagaaagcgg  | gtccaaatgt | gattcaaaac  | actgtacgga | 960  |
| gtggcatatt | agaattgccc  | taaactgaac  | tgcaataaat | tatgtgtgta  | tgtatatgtg | 1020 |

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| tgggaaagag | aatgtactgt | atatgtgtat | gttatacaga | catatacaca | tacatacatt | 1080 |
| gacccacagg | acattgtaaa | atattatcac | atgacatctt | aagtagaaat | aagtagggac | 1140 |
| ttttattcca | tccttttttt | cacgtttaca | ttttaattat | tacaagttgc | tcctgcccc  | 1200 |
| tccttgaact | atgttggtgt | gtgtatatca | ctgctttata | taagttattt | tttaaggtga | 1260 |
| actcagatgt | tatggttttg | taaatgtctg | caatcatgga | taggaataaa | atcgcttatt | 1320 |
| tgagagcttt | cattaaaaaa | aaaaaaaaaa | aacttcgagg | ggggggcccg | tacccaat   | 1378 |

&lt;210&gt; 81

&lt;211&gt; 1440

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1128)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1129)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1440)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 81

|             |             |            |            |             |             |      |
|-------------|-------------|------------|------------|-------------|-------------|------|
| actttgtcca  | aatgtgtctg  | tcacatgtag | tcagctgnag | naatttaaaa  | tgaattgcca  | 60   |
| agtgaagagt  | ctgtggatta  | attggccggt | aattaacagg | ctttatcaat  | gtgtcctcaa  | 120  |
| gggagaggcc  | caaccctaata | taaggagcta | aacttcctga | gtgaggggct  | gtgaggatgg  | 180  |
| agggtggagga | ggcatctggg  | gcgggtggtg | gccgggccag | cagatggcgc  | ctccctggct  | 240  |
| gagctgcccc  | caccgccagt  | tcctcattt  | ccactcagga | aggcagagaa  | ggcagagtga  | 300  |
| tctcctcaag  | gaagagcttc  | cccagccttc | gggagcagct | ggcagggcgt  | ccgggaataa  | 360  |
| gccctacacg  | ccgccgcctg  | cctccaactc | actaaccctg | cgcctcttgt  | ctttcagatt  | 420  |
| caacgcgttc  | aacagaagcc  | atccccagcc | cagcttaaat | tataaagata  | gacaataaact | 480  |
| ctgttccaat  | ctgcgtgggtg | cttctttagt | aaatactgta | cagattttac  | catggagaac  | 540  |
| ttttttttta  | gttttttact  | tttcttaatt | acccttattc | cgaatggacg  | aacactttct  | 600  |
| accactgctg  | accattgtaa  | aataccgtgt | atataaatcc | cattgaaata  | atgccctgga  | 660  |
| atagaacatc  | tcaaatgctg  | cttaattaca | gactcaggtc | gattacttgt  | atttcatgta  | 720  |
| atgttcctcc  | aagttagaca  | tctggtgcaa | gaccaaccgg | gagaccatgg  | aattgtcaaa  | 780  |
| agtacaaaact | gacagtgtgt  | atatttaatt | taaagactta | tttaaaaact  | cacaagctct  | 840  |
| cacctagact  | ttggagagca  | gtctgttttc | tgtaatgtct | gatactagaa  | actaatttgc  | 900  |
| ttatttttagt | tgtattcaag  | atgtgaagat | gtattttata | gacaagttct  | gtttttgaac  | 960  |
| tttgtggaac  | tgattccaatc | aatcaatttc | ccagttatga | tgagtattta  | cattatgaat  | 1020 |
| gtataacccta | gacatgattt  | gtaaagccga | cagtatgttt | ctattacaca  | acactttttg  | 1080 |
| atacagcgtc  | tcttgtcttc  | actgatactg | gagtctccgt | tgtctgcnnng | gtcccttcga  | 1140 |



|            |            |            |             |            |            |      |
|------------|------------|------------|-------------|------------|------------|------|
| gtttctagtt | acagacacaa | tcatactgtg | attttatttt  | taatattgat | atgctatcaa | 1200 |
| actgtgatac | acttataatt | cactggtcct | gcatacaggag | atggagtggg | gaaaactgta | 1260 |
| tttaatacag | tttgtatctg | aataatctgt | atggtttata  | cagtttgtgt | tgttcagaga | 1320 |
| tgtttaaagt | ttgatctttg | tttttctaaa | gattaaaaaa  | gcacttgccc | cactgtaaat | 1380 |
| atacagcatg | taaaatttct | rtagtatata | aatggcagca  | aatcacaaaa | aaaaaaaaan | 1440 |

&lt;210&gt; 82

&lt;211&gt; 1381

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1379)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 82

|             |              |            |             |            |             |      |
|-------------|--------------|------------|-------------|------------|-------------|------|
| cccggtctgc  | aggaattcgc   | yacgaggcca | gcagttgctc  | ccagttcagg | aggtgctcct  | 60   |
| gtaccctggc  | cacagcccaa   | tcctgccact | gctgacatct  | ggggagactt | taccaaactc  | 120  |
| acaggatcaa  | cttccagcca   | gaccagcca  | ggcacaggct  | gggtccagtt | ctgacctgag  | 180  |
| cacggttttt  | cctcatgtga   | cttctgggaa | ggcgctccct  | catctgggcc | aaaggaagga  | 240  |
| ggacgaagcc  | ctcctcagct   | ggcctgtgtt | tggggcatga  | atctctcctc | tcctccttgt  | 300  |
| ctggctctgt  | tgacaaaccg   | ggcatgtttg | gcagtaaatt  | ggcacctgtg | cacactgttt  | 360  |
| cctgggattc  | aagtatgcaa   | ccagaacaca | ggagaagaaa  | agctccagga | tccctgtccc  | 420  |
| catctgtcct  | cttgatgtga   | gagagactct | gagacttctt  | ccatcgcaat | gacctgtatt  | 480  |
| aaacacaagc  | cccccaagca   | aaagaagagg | ttgagtttgc  | tgccaggatt | cagatcagcc  | 540  |
| cttccagggg  | tctgcagggtg  | tcacatgata | acagttcagc  | gggaggcttt | ccgtacccac  | 600  |
| actggctgta  | gcacttcagt   | ccatctgccc | tccagaggag  | ggtttcttcc | tgatttttag  | 660  |
| cagggttaga  | ggctgcagct   | tgagctacaa | tcaggaggga  | aattggaagg | attagcagct  | 720  |
| tttaaaaatg  | tttaaatatt   | ttgctttgct | aatgtgctga  | tccgcactaa | ctcatctttg  | 780  |
| caaaaggaac  | tgctccctcg   | gogtgcccca | gctggggcct  | ctgaagggat | tcctcactgt  | 840  |
| gggcagctgc  | cctgagcttc   | aggcagcagt | gttcatctct  | ggccagttgt | ctggtttcca  | 900  |
| tgtattctag  | gccaggtagg   | caacacagag | ccaaggcggg  | tgctggaagc | cagacggaac  | 960  |
| agtgttgggg  | caggaaagggtg | gatgctgttg | tcattggagct | gtgggagttg | gcactctgtc  | 1020 |
| tgctgggtggc | cctctcggct   | cacatgttca | cagtgcagct  | cctggcagac | ttgggttttc  | 1080 |
| tctttggtgg  | tttctaaagt   | gccttatctg | caaacaactt  | cttttctcct | tcaggaaactg | 1140 |
| tgaatggcta  | gaagaaggag   | ctcagtaaac | tagaagtcca  | gggttgcttg | gtttactggg  | 1200 |
| ttataagaaa  | tctgaaagca   | cctctgacat | tccttttatt  | aactcacctc | tcagttgaaa  | 1260 |
| gatttcttct  | ttgaaagggtc  | aagaccgtga | actgaaaaaa  | gtgttggoct | ttttgcggga  | 1320 |
| ccagattttt  | aagataaaaat  | aaatatTTTT | acttctgtca  | aaaaaaaaaa | aaaaaaatnt  | 1380 |
| c           |              |            |             |            |             | 1381 |

&lt;210&gt; 83

&lt;211&gt; 1706

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 83

|             |             |            |            |            |            |     |
|-------------|-------------|------------|------------|------------|------------|-----|
| actgcaccac  | tgcccagggtc | tcccggctgg | atgaagacgt | ggcccatgag | gaagctggct | 60  |
| agctcagact  | ggagagtagc  | ttcaggaaaa | aagacaagtg | gcctaaggaa | atcacggccc | 120 |
| ccaactatca  | tctgagggtc  | aaagatgaga | agtagatcac | ttaataagac | aaaagcctgt | 180 |
| agggggaaaa  | gaaaggatgt  | ttaaaaggac | agaatgtttc | ccaaggtaga | aatgacactg | 240 |
| tcaattttctc | cttggaatgg  | gggcagggat | actcgccttg | ttgctcccac | ttgagtcagt | 300 |
| actcacctgc  | tcctggatct  | cagtatccac | atctgagagg | caactctggc | agagttcaca | 360 |
| gaaggccacc  | attctgtccc  | tcaaactcga | cagctgcttc | tgtgggcaca | gtggcttgaa | 420 |
| ggggaagaat  | gaagacacag  | actcctctgt | tcccattatc | ccatctaaga | cccacactca | 480 |

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cctggggaag  | catctgattt  | agaaatgtgg  | gttagtgtcc  | agagaatgga  | aaaatagaca  | 540  |
| agagtcaagg  | ctggcaggat  | aacctgtaac  | aacaaagggt  | ttgaaaaatg  | agggtttgggt | 600  |
| taggagaggg  | agagacagat  | agccagaaaac | acaccagtga  | agaggagaga  | aaatgagtaa  | 660  |
| agggagagct  | aattcctttt  | ccagtggaaa  | atgagtgata  | ttctggacat  | tcttcagagg  | 720  |
| catctacacg  | aagtagaaat  | gtcaccgctc  | cctaatttac  | tctacgtctt  | ctagaatccc  | 780  |
| tcaatattat  | ccttggcttc  | caggaaatcc  | aagaagaccc  | tggagtaga   | gtccaccttc  | 840  |
| taagagagga  | atgtaagagg  | tgaacccccac | ccacctgatc  | ttcctcgctt  | tgtccactcc  | 900  |
| acgcactgag  | acttgacaca  | cctagtggcc  | acctagaacg  | taggtcctta  | aaatytagcc  | 960  |
| ccccagcccc  | caacccatct  | ctagcctgtc  | cactcacctg  | gtgaggaacy  | tytcctgtgt  | 1020 |
| ccacagcytt  | ctgcaggagt  | tggcaacatg  | gctcatagag  | ctcccagcga  | gtcagggtcat | 1080 |
| gagtgccttg  | ggggagaaaag | gggaatgtta  | tactggaaaa  | gaacagaggg  | aaccaactcc  | 1140 |
| acagacacca  | gtaaaaacgg  | gatggggaaag | aggaggaaaag | ccactcactt  | gtagaaggca  | 1200 |
| gagagggcgtt | tcagagtggc  | tgccagatta  | tatacctcat  | cctcatctag  | gaaggacgac  | 1260 |
| tgagaaggaa  | agaagatcca  | caatagcatt  | tccccagaa   | ctcatcagtc  | cacatcccc   | 1320 |
| gtcttgacgc  | ccctcccacc  | cttgtttggg  | gtgtcccatt  | gtccagcccc  | agctcctacc  | 1380 |
| tgtaacagct  | cttcaagctc  | ctgctggaar  | cggtcagtc   | gcaaactctac | tagctggctg  | 1440 |
| cgggcaaagt  | cgcgccggct  | gaagaaagtg  | aattcgggat  | tacagagcag  | gtaagagcat  | 1500 |
| gcgccccagc  | ctcaagcacc  | gctggctctg  | catgcttcac  | caccacctcc  | tggagttgct  | 1560 |
| gcaggaaacag | ctccaggtgc  | tgagaagaaa  | aggcagaaga  | tgggtgtgctg | tggggatggg  | 1620 |
| aggaggacac  | tcttctggcg  | ggaggtgga   | cgggggttaa  | agcattaaac  | ttcaaggata  | 1680 |
| agatgcctaa  | raaaaaaaaaa | aaaaaa      |             |             |             | 1706 |

&lt;210&gt; 84

&lt;211&gt; 573

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 84

|            |            |            |             |            |             |     |
|------------|------------|------------|-------------|------------|-------------|-----|
| gaattcggca | cgagcttggg | agccttagaa | ctgcatgagc  | tgctttacca | ctgggaaaca  | 60  |
| cgagcacagc | ctagcttgat | tttgtatgtg | gtatcagatc  | taagggtgat | ggaattcagg  | 120 |
| acttcctgtc | tactctttga | ttttgtttta | tttttagaaa  | tgttttattt | tgttttattc  | 180 |
| atttattcat | cttcagagac | atggtctggc | tctgttgccc  | aggatggagt | gcaggtgtgtg | 240 |
| atcataggcc | actgcagtgt | tgagctcccg | ggctcaggcg  | atcctcctgc | ctcagctycc  | 300 |
| ttagtagctg | ggactatagg | cacatgccct | accatgcctg  | gctttgtcta | ctttttgaat  | 360 |
| gatgtcycaa | actagaagg  | ctattaattt | aaaaaattaa  | ggatagcatg | ccataattaa  | 420 |
| aaataataac | agtgggaaaa | ggcaccttcc | aattgattcag | acatcaactt | gtgattttaa  | 480 |
| aaaacgaaaa | ataataataa | ggaaaaaaag | gggaaaaagt  | taaataaaaa | taaaatttaa  | 540 |
| aaaaaaaaaa | aaaaactcga | ggggggcccc | gta         |            |             | 573 |

&lt;210&gt; 85

&lt;211&gt; 684

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 85

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ctctttggct | gtgtctacct | ccttcatctg | ctgcgcgcag | ataagcaccg | ccctgcccct | 60  |
| aggctccagc | cgtcccgcac | cagcccccag | gcaccgagag | cacgagcatg | ggcaccaagc | 120 |
| caggcctccc | aggctgctct | ycacgtccct | tatgccacta | tcaacaccag | ctgcygcccc | 180 |
| gctacttttg | acacagctca | cccccatggg | gggcccgtcc | ggtgggcgtc | actccccacc | 240 |
| cacgctgcac | accggcccca | gggcccgtgc | gectgggect | ccacacccat | ccctgcacgt | 300 |
| ggcagctttg | tctctgttga | gaatggactc | tacgtcagg  | caggggagar | gcctcctcac | 360 |
| actgggtccc | gcctcactct | tttccctgac | cctcgggggc | ccagggccat | ggaaggaccc | 420 |
| ttaggagttc | gatgagagag | accatgaggc | cactgggctt | tccccctccc | aggcctcctg | 480 |
| ggtgtcatcc | ccttacttta | attcttgggc | ctccaataag | tgtcccatag | gtgtctggcc | 540 |
| aggccacact | gctgcggatg | tggctctgtg | gcgtgtgtgg | gcacagggtg | gagtgtgtga | 600 |
| gtgacagtta | ccccatttca | gtcatttctc | gctgcaacta | agtcagcaac | acagtttctc | 660 |

tgaaaaaaaa aaaaaaaaaa aaac

684

<210> 86  
 <211> 1036  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1020)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1024)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1032)  
 <223> n equals a,t,g, or c

<400> 86  
 tggaggcaga tgcacaggag aaaggttccc gtccgcaccc tctcagacct gaggctgagc 60  
 ttgcagttag ggcttctcct cgccccctcg cccgccccca gagctgccat cctgctggt 120  
 acaagccaga ggagcccga tgtgaggccc cagatcacct ccagggactt ggggttccca 180  
 tctgaaatcc ttatttttg taccatgggg tgggcccccg gctgagaagg aagaagcacc 240  
 ctctccccgg cctcctctgt ctgcacccgt ggggctgtga cttactcctg cctccagggg 300  
 cggggcgggg ccccttggga cctcttaagg cccaaggtgg gccccaggac ctytgggcag 360  
 agtggaytgc tcatggcaga tgtgtggcaa tgtctggctg wgtctttccg gcamctgcgt 420  
 yccctytccc ggytccccct gctgcatggt ggatgtgctc cttcctggcc cggtcacatt 480  
 gcctccttga gccttagtcc agggggtcac tyctcccacc ccacctacct cacagggttg 540  
 ttgtgagggt gcacagagga gcaaagtccc tgaaggccct caggcagtat ataggggccc 600  
 cccaccttca gctgccctgg gatgggaagg acccagcccg acccctgggc ataactgt 660  
 gtttgcaaat ggagattcag gtattgggga tgcaggttgt ggggagctgg cctggcagag 720  
 taggggtagt tggcttggcc ttctctttgg tgatccacc cccagccatt tgcattgctg 780  
 gccagcgcc tggcctgggg ggcggggaga ggcagcagaa ggggctgggc aggggcggtg 840  
 gaggactcag gaactgcccg gggagagtgg gtatggcggc tgagccaggg gccctcctgt 900  
 gtttgacttc cgggatggg tccttgcttc tcagctgtgt ccgacccac catgtaataa 960  
 aacccaaagg aacagcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020  
 ccnsgggggg gncccg 1036

<210> 87  
 <211> 908  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (805)  
 <223> n equals a,t,g, or c

<400> 87  
 ttaaacaaat ggaatcatgc aatatgtgac cttttgcgtc tggcttattt tatttagcat 60  
 aatgtttttg aggttcatcc aagctgtagc atgtatcagc acctcatttc tttttctggc 120  
 tgaatattat tccattatat ggatttacca caattcattt acctattcat cttttgtttc 180

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| tgctgtctgg | ctattgtgaa | taatgcttcg | ataaacattc | atatacaagt | ttctatgtgg  | 240 |
| ctttatgttt | tcatttctct | tggctatcta | catgggagta | gaattctagg | tcataatata  | 300 |
| attttatgtt | taacttctca | aagaattgcc | aaaaggtttt | tcatagtggc | tgcattcattt | 360 |
| acattccac  | cggcaatgta | caaggatttc | tatttttcca | tatccttgca | cttaccaaca  | 420 |
| cttctttttk | gtwatwattt | tgttttttca | ttattgccac | cctagtggat | gtgaaatggc  | 480 |
| atcttattgt | tttgatttgc | atcttcttaa | tgacaaatga | tatcatactt | tttttatgtg  | 540 |
| cttacggatc | aaaggtattt | ccttgagaa  | atgtcccttc | aagtcctttg | ccatttcaaa  | 600 |
| atttggttat | ttgtctttta | ttattcagtt | ttaagaaatt | ctggccaggc | gcagtggctc  | 660 |
| acctgtaatc | mtagcacttt | gggaggccaa | ggcgggcaga | tcacttgagk | tcaggacttc  | 720 |
| gagaccagcc | tggccaacat | ggtgaaaccc | catcttacta | aaaatacaaa | aattagctgg  | 780 |
| gcgtgggtgg | aggtgcatgt | aatcntatct | actcaggagg | ctgaggcagg | agaatcgctt  | 840 |
| gaaccagga  | ggcggaggct | gcagtgagcc | aagatcacgc | cattgcactc | tagcctgggt  | 900 |
| gacacaga   |            |            |            |            |             | 908 |

&lt;210&gt; 88

&lt;211&gt; 655

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 88

|            |             |             |            |            |            |     |
|------------|-------------|-------------|------------|------------|------------|-----|
| tgacttggtt | ccttctcccc  | agcaaatact  | gccttcttgt | ttttctctga | tgtggcaggt | 60  |
| gactacaaaa | tccgccttgg  | tattcttcaa  | atgcataat  | attcctttct | tgtcagctcc | 120 |
| ctctcttctc | agattagaaa  | actgcctcat  | tttctgtcca | ctggatgtgc | agtcccagct | 180 |
| tgtcttctct | tcctcccccc  | ctgttgacgg  | tgttcttttt | tttttcttct | tctccccact | 240 |
| gggcagcaaa | agttgttcca  | cagtggaaaaw | ttaggcatcc | tcaagtttcy | tcccagcttc | 300 |
| tgctgtgttt | tcttagagta  | aattgccaat  | ttctgttttt | acaggaaatc | cttttttaaa | 360 |
| aatggaatca | gtgtgggtccc | catctactct  | gcaaaaattg | catttttctc | tattttcaaa | 420 |
| tgagatttgt | tcaagtttca  | aaaccacgtg  | aaataataaa | tgtatagtag | ttttcttttc | 480 |
| cttgggcatt | gctwgatatg  | tgaatgggtt  | ttatgaaaaa | taataaaatc | ataacgctat | 540 |
| ttgtttgact | ttcaatttca  | tgggaatttt  | tctcagctaa | actctaaatg | gtgattargc | 600 |
| aaaaaaaaaa | aaaaaaaaacy | gragggggggc | cgggtacca  | ttcgccctat | aatga      | 655 |

&lt;210&gt; 89

&lt;211&gt; 1102

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 89

|            |            |             |            |            |             |      |
|------------|------------|-------------|------------|------------|-------------|------|
| tttttttttt | accattttaa | ataaaatgaa  | agtgaacctc | tgtttataaa | aatctttgtc  | 60   |
| tgcatctctg | cttatttctc | tagaagagat  | tccaagaagc | ggtgagtgat | ttcacggcag  | 120  |
| cagaggggtg | ggacatatta | cgggcgcgga  | tccctcttgg | agtgagatga | ctctccggag  | 180  |
| agatttagtc | gtcaccctcg | cgtgtgaggg  | tgcgtcacac | cccagggatg | tgtctatcaa  | 240  |
| gatggaagat | cttttacacg | ctcttgattt  | tgtttgcctt | tttttctatt | actagtgaga  | 300  |
| atgaaacttt | ttatatgatt | attatccatc  | ataatccaac | acaaattact | gcttcatgtt  | 360  |
| cttttacttt | cctgtgaagg | tttttagtgcc | ttttaaaaat | tgctatata  | taagcttgtt  | 420  |
| aatacttcca | tgtctgtatt | gtggccatca  | gtttccccgg | gcacaggcct | gcacattttg  | 480  |
| ccttcacacg | ctgggtgggt | tttcaatttc  | acttctattt | ctcgttcttc | tatcgtttta  | 540  |
| tgttcagacg | ggtttctccg | tgtagaaagc  | agtttatgaa | gatttacttt | cgacagtctt  | 600  |
| ctctctactt | tctacagtga | attctctgay  | gtgtctggga | gtwtgggggt | ctgggtaaga  | 660  |
| rtctctctct | cacctatttc | tctattacga  | tccacagcct | catgctttat | garattgggtg | 720  |
| gccgggarcg | ggggagattt | gcggatcccc  | caagccagac | tttatcccc  | tatccctgcc  | 780  |
| tctggatccc | acgtacaggc | ctgggaactc  | cctgtgggta | ggggccaatg | gtctcgcact  | 840  |
| ctcacctgta | ccccagggtc | ggcaccaggt  | ggtcaaggag | agaggctgcc | caagcgcac   | 900  |
| cytctgggtg | ccccctgaca | cgcctccaaa  | gtgagcaggt | aggtttcaac | agccccacgt  | 960  |
| tgcaggtggg | agatgaagct | cagggtggag  | accagtatct | cacagttctc | tttgcattggc | 1020 |
| cgggtacttg | ttagtcaact | gatcaagtga  | aaattctagc | cccagaggca | ggagaatccg  | 1080 |

gaacaaaatt aaaccagcca gg

1102

<210> 90  
 <211> 1533  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (12)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (123)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1522)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1527)  
 <223> n equals a,t,g, or c

|   |      |
|---|------|
| <400> 90  |      |
| ggcagcagcc gncacgggca ggcggccata ggcgcaggga cccctctggca gcgggagccg  | 60   |
| cgggtcgagg ttatggatcc agcggggcggc ccccgggggcg tgctcccgcg gccctgccgg | 120  |
| tgcttggtgc tgctgaaccc gcgcggcggc aaggggcaagg ccttgacagt cttccggagt  | 180  |
| cacgtgcagc ccttttggc tgaggctgaa atctccttca cgctgatgct cactgagcgg    | 240  |
| cggaccacg cgcgggarct ggtgcggctcg gaggagctgg gccgctggga cgctctgggtg  | 300  |
| gtcatgtytg gagacgggct gatgcacgag gtggtgaacg ggcttcatgg agcggcctga   | 360  |
| ctgggagacc gccatccaga agccctgtg tagcctccca gcaggctctg gcaacgcsct    | 420  |
| ggcagcttcc ttraaccatt atgctggcta tragcaggtc accaatgaag acctcctgac   | 480  |
| caactgcacg ctattgctgt gccgcccggc gctgtcacc atgaacctgc tgtctctgca    | 540  |
| cacggcttcg gggctgcgcc tcttctctgt gctcagcctg gcctggggct tcattgctga   | 600  |
| tgtggacctg gagagtgaga agtatcgccg tctgggggag atgcgcttca ctctgggcac   | 660  |
| cttctcgct ctggcagccc tgcgcacct cgcggccga ctggcctacc tccctgtagg      | 720  |
| aagagtgggt tccaagacac ctgcctcccc cgttgtggtc cagcagggcc cggtagatgc   | 780  |
| acaccttggt ccactggagg agccagtgcc ctctcactgg acagtgggtg cgcagcagga   | 840  |
| ctttgtgcta gtcctggcac tgctgcactc gcacctgggc agtgagatgt ttgctgcacc   | 900  |
| catgggccgc tgtgcagctg ggcctatgca tctgttctac gtgcgggcgg gagtgtctcg   | 960  |
| tgccatgctg ctgcgcctct tccctggccat ggagaagggc aggcataatg agtatgaatg  | 1020 |
| ccctacttg gtatatgtgc ccgtggctgc cttccgcttg gagcccaagg atgggaaagg    | 1080 |
| tgtgtttgca gtggatgggg aattgatggg tagcgaggcc gtgcagggcc aggtgcaccc   | 1140 |
| aaactacttc tggatgggtca gcggttgctg ggagcccccg cccagctgga agccccagca  | 1200 |
| gatgccaccg ccagaagagc ccttatgacc cctggggcgc gctgtgcctt agtgtctact   | 1260 |
| tgccaggacc ttcctccttc cctagggtcg cagggcctgt ccacagctcc tgtgggggtg   | 1320 |
| gaggagactc ctctggagaa ggggtgagaag gtggaggcta tgctttgggg ggacaggcca  | 1380 |
| gaatgaagtc ctgggtcagg agcccgctg gctggggcca gctgcctatg taaggccttc    | 1440 |
| tagttgttgc tgagaccccc accccacgaa ccaaatacaa ataaagtgc attcccaaaa    | 1500 |
| aaaaaaaaaa aaaaaaaaaa anccccnggg ggg                                | 1533 |

&lt;210&gt; 91

<211> 575  
 <212> DNA  
 <213> Homo sapiens

<400> 91  
 atcctctgga atctagggtg aagccaccaa gccttcttca cacttgcggt ctgagcatct 60  
 gcagacttaa ccccatgtgg caatcaccaa ggcttatggc ttgtgtcctc cagaactgtg 120  
 gccagagctg tacctggggc cctttgagct gaggtggaag ccagagtctg aagctcagca 180  
 gggcagtarg gccctggggc tggccctga aaccattctt ttctcctaag cctctggggc 240  
 ttgatggga rgggtgtcc tcaagatttt tgaaatgcct ttggagggtt tttgccttgt 300  
 ctgggatatt ggcttccttt tagttatgct catctctcta gcaagtgaat gtttcacaac 360  
 ctgcttggat tctttctcta ccacagarcc aggtgcgaaa ttttacaac ttttactc 420  
 tggttccctt ttaaatataa atttcaatgt taagtcaact ctttgctccc atatctgatt 480  
 taggttgctg gaagtagcca agtcacctct tgaatgcttt gctgcttaga aatttcctct 540  
 actaggtagc ctgggtcatc acacttaagt tcaaa 575

<210> 92  
 <211> 639  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (126)  
 <223> n equals a,t,g, or c

<400> 92  
 tcctttcatc ttaagcacca cccgacaggg caggtaactat taccatctcc gtttgacaga 60  
 tnaggaacct ggcacaggaa gcatttaagt ggattcccca ggatcgcccc actgtcagga 120  
 gcagantcag aatgggcctc agcatcaggg tcccaatcct ggcttctaac tgctgcgctc 180  
 tgcccttcyc tcwccccacc tccccactcc agtgcctttg gtcatgccac tgcagcttcc 240  
 aggccaatac tggattagcc tcttagtggt cttgtccctg cagccatttc cccaggcagc 300  
 aattccatgt gccctcactg atgtagggtg ctcttggtgc atttgtcaca tcctattgaa 360  
 ttgtttatgc atcttggtca cactcacagc accctccctc tcacacgtcc tcctataaa 420  
 aatgtccctc agtgtctgct atgagccagg tgcagactta agtgacaggg ctgctacggg 480  
 aaataaaaaa ttaacaagga gcacctgcct cttaatgcac agtaacaaac tatgttaagt 540  
 gtcaggaagg aaagggttaag gatgccagga aggcctttta taaataacct gacttagatg 600  
 ggcagggtgt gctgargatt aagaacgtgt tcttctoga 639

<210> 93  
 <211> 858  
 <212> DNA  
 <213> Homo sapiens

<400> 93  
 cccccgggct gcaggaattc ggcacgagag tggctggagt ctggctgcag agggaagaca 60  
 tcagcaggga gggagccagg gcctgtcaca tctttcctct ggccattgtc ctggtctttg 120  
 taagcccaga atctcccctt ccctgaaggg aggcacgac cccaggaggg cagcaggtgt 180  
 gctgtgaggg ttggagtagt gtgagaggtc aggttacact agaattggcca tggacaccat 240  
 gtgggggtgc tctgggctgg gccacagaa agtgtccttc ctgctgctcc tcccctgcag 300  
 cttccccga ccttggtggt tatttggttt gataccaatc agcagacctt gcaagggtga 360

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ggctcccagg | cctctcagtc | ccaccactct | catgtgccag | tcacccctac | tgtaactgcc | 420 |
| caatgagtag | ttcttgccca | ctgccaagat | agagccagtt | taccaagaca | ggggaattgc | 480 |
| agtagagaaa | gagttgaata | tacatagagc | cagctaaatg | ggagagtggg | gttttcttat | 540 |
| tacttaaate | agcctcccc  | aaaattcaga | ggtgagaatt | tttcaaggac | agtttggtgg | 600 |
| gcagggccta | gggaatggat | gctgctgatt | ggctagggat | gcaatcatag | gggtgtagaa | 660 |
| aaggctcctg | tgactgagtc | ccacttttgg | gtgagagcta | ccaaggagct | gctggtctgc | 720 |
| tggtcccggg | agagccatct | ggtgtcagga | atgcaaaagt | gtggccaggc | acagtggccc | 780 |
| acacttgtaa | tcctagcact | ttgggaggct | gaggcaggag | gaatgcttga | gcccaggagc | 840 |
| tcgagggggg | gcccggta   |            |            |            |            | 858 |

&lt;210&gt; 94

&lt;211&gt; 526

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 94

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gcaggggaat | tcggccacgg | aggggtttca | acagggcccg | tggggtgagg | tgcaracaca | 60  |
| aagcccataa | gtgctggcct | gttgggacaa | atgagagaaa | tcccataggg | tggtgatgac | 120 |
| agcgcaytca | gccatcytay | tcctggggaa | aatgaaactt | gtgctcctat | caaatgctca | 180 |
| gttgtaaaac | tggaaaaaaa | ttttagaaga | catcttgtcc | agcatctgtg | tttatgtcta | 240 |
| taaaatgtag | aaaactaaag | cacagagatg | ttaaatgttt | tgtccaaggt | ccaacagctg | 300 |
| gttagcargc | ttggtctggg | gacctttcta | ctgaaccaca | gtgccgctgg | gggaagtcct | 360 |
| cagcacagat | ggctgctgct | atagctgggg | tatgggcagt | attagtagtt | aaccagtcaa | 420 |
| cccaagttcc | catagtctag | gttctgcttc | agctggaggt | tagggaaaaa | cacaagaaaa | 480 |
| tcctttacca | ctctaccagt | gctgggggat | gtactaagag | atcccc     |            | 526 |

&lt;210&gt; 95

&lt;211&gt; 426

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ggcacagggc | aggagagact | tggtccatgg | ggagaagcct | gcagtataga | tgggacctcc | 60  |
| aggagcccaa | gtagcataga | ccctgctgat | ccggggccat | tgagccagag | gatttgggct | 120 |
| gaatgtcccc | agagacaaaa | gggaaaggta | gaccccttcc | cttaaagatg | aaagccatcg | 180 |
| cccgggcttg | cttattgctc | tctctcctgg | tccttccaca | tgttggttct | gaacatttgt | 240 |
| tctggcatca | caatccccgt | catcctgtca | tctggccctt | cccacctttc | caccttatct | 300 |
| cttgacagt  | ctccgcgtcg | acctggcacc | tgggtgaarg | cttgctcttg | ctggtgccca | 360 |
| tagccccag  | tgtatggtct | tgamctcccc | agccatatgg | aracccacct | caggagggcc | 420 |
| cctcga     |            |            |            |            |            | 426 |

&lt;210&gt; 96

&lt;211&gt; 844

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (416)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (471)

&lt;223&gt; n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (490)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (732)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (835)  
 <223> n equals a,t,g, or c

<400> 96  
 ggcacagcgg cagcagatag gaagcttggc aggggcagct cccccagtgc gcattgccct 60  
 gtaactcgag cgcctgggag tggggagagg ctgggaaatg gagcaggggtg gtggacctcg 120  
 tcttctcctg ctcaccccag gcctcctcca taacacctac ctagcacggc ctggggactt 180  
 cccagcccaa ggaacaactg agaatactga gtgccagggt agccctagcc ccatttcaca 240  
 cctgggcaaa gtgaggtcac tggattcaaa cactcagatt taaacctcct ctgtgtctgc 300  
 agcacctgta tataactgcc agcctctgct gcccctctcc aaaaagtctc tgcccttgctc 360  
 tttggcacct gtctctgtcc tccccattct ctgctcctcc tttctccaac tcagantcac 420  
 cctgttagtt cagcaaatgt tcatcgagct ccataatgta gcaggacagg nctgtctaac 480  
 agattctggn cttgcaaggg tgagacaagt actctccatc tttctctcat cttcacagat 540  
 ggtctgctca acaactttgc actgaattgt aaataattga tactgcataa aacattgatg 600  
 ttctttaagg gtagtcacgc aagggtggcaa gtcttataat gataactgct caaggatctc 660  
 tcagtgaagc atttggggst gctagctctg cctatgggtg aggtcagcta tctcacgcca 720  
 tctacttcca cntgcccccc catgccaggc tcacctgag ctgagatgcc tgagcaggtg 780  
 gcagaaagga gccacctggt ttatgcttcg ggaccacaaa ctctctatc cagangacag 840  
 tttt 844

<210> 97  
 <211> 1985  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (332)  
 <223> n equals a,t,g, or c

<400> 97  
 agccctgctg aagtacaggt tcttctatca gtttctgttg ggcaatgaac gagcaacagc 60  
 aaaggagatc agggatgaat atgtggagac gctgagcaag atttacctgt cttactaccg 120  
 ctcttacctg gggcggctca tgaagggtga gtatgaggaa gtcgctgaga aagatgatct 180  
 aatgggtgtg gaagatacag caaagaaagg attctyctca aagccatcgc tccgcagcag 240  
 gaacaccatt ttcacctag gaaccgcgg ctctgtcatc tccccactg aacttgaggc 300  
 ccccatcctg gtgcctcaca cagcgcagcg gnagagcaga ggtatccatt tgaggccctc 360  
 ttccgcagcc agcactacgs cctcctagac aattcctgcc gcgaatacct tttcatctgt 420  
 gaattttttg ttgtgtctgg ccagytgca cagcactgt tccatgctgt catgggcccgt 480  
 acactcagca tgaccctgaa acacctggat tcttatctag ctgactgcta cgatgccatt 540  
 gctgtttttc tctgtatcca cattgttctc cggttccgta acattgcagc aaagagggat 600  
 gttcctgccc tggacaggta ctggggaaca ggtgcttgcc ttgctatggc cacggtttga 660  
 actgatcctg gagatgaatg ttcagagcgt ccgaagcact gacccccagc gcctaggggg 720  
 gttggatact cggccccact atatcacacg ccgctatgca gagttctctc ccgctcttgt 780



|             |            |             |             |             |            |      |
|-------------|------------|-------------|-------------|-------------|------------|------|
| cagtatcaac  | cagacaattc | ctaatagaacg | gaccatgcaa  | ttgctgggac  | agctgcaggt | 840  |
| ggaggtggag  | aattttgtcc | tccgagtggc  | agctgagttc  | tcctcaagga  | aggagcagct | 900  |
| tgtgtttctg  | atcaacaact | atgacatgat  | gctgggtgtg  | ctgatggagc  | gggctgcaga | 960  |
| tgacagcaaa  | gaggttgaga | gcttccagca  | gctgctcaat  | gctcggacac  | aggaattcat | 1020 |
| tgaagagttg  | ctgtctcccc | cttttggggg  | tttagtggca  | tttgtgaagg  | aggctgaggc | 1080 |
| tttgattgag  | cgtggacagg | ctgagcgact  | tcgaggggaa  | gaagcccggg  | taactcagct | 1140 |
| gatccgtggc  | tttggtagtt | cctggaaatc  | atcagtggaa  | tctctgagtc  | aggatgtaat | 1200 |
| gcggagtttc  | accaacttca | gaaatggcac  | cagtatcatt  | cagggagcgc  | tgaccagct  | 1260 |
| gatccagctc  | tatcatcgct | tcacccgggt  | gctgtcccag  | ccgcagctcc  | gagccctccc | 1320 |
| tgcccgggct  | gagctcatca | acattcacca  | ccttatgggtg | gagctcaaga  | agcataagcc | 1380 |
| caactttctga | tgtgccagaa | accgcctga   | gatctgccgg  | tcactctccat | ggacttctgc | 1440 |
| accccatcc   | atacccttct | tcacctgggg  | tacccttcc   | agttttcccc  | ttgcttccc  | 1500 |
| ggcccttgac  | atggcttacc | tgcccttact  | cccagcacct  | tgcccaacag  | gataagctgg | 1560 |
| atccccttgg  | ccttctgaat | atcccagtg   | cttcagggtt  | cccaagacca  | cttccctgtg | 1620 |
| ggcttccaaa  | atggccttta | tcattttctc  | agtctgtcac  | cctcctttcc  | tgctcccata | 1680 |
| caccaaggc   | ttgtttcttc | ccctgtaaaa  | accactgcct  | caatctctgg  | ttcactcaac | 1740 |
| tagtcacat   | gtcctgaggg | atgaagcctc  | ctcagctctt  | ggaattgctg  | gcaaggggtg | 1800 |
| actgcctctg  | agtcattgtg | tttttcaaag  | tgattttctt  | tctgtagctt  | tttgacctaa | 1860 |
| gatctcagca  | atttgaacac | taacctctcc  | cctcctggct  | caagaattac  | tccgaagtca | 1920 |
| gtctgcagaa  | aataaatatt | tagtatgaca  | tgaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa | 1980 |
| aaaaa       |            |             |             |             |            | 1985 |

&lt;210&gt; 98

&lt;211&gt; 1416

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| atatgaagg   | aaagaatttg  | attatgtttt  | ctcaattgat  | gtcaatgaag  | gtggaccatc  | 60   |
| atataaattg  | ccatataata  | ccagtgatga  | cccttggtta  | actgcataca  | acttcttaca  | 120  |
| gaagaatgat  | ttgaatccta  | tgtttctgga  | tcaagtagct  | aaatttatta  | ttgataacac  | 180  |
| aaaagggtcaa | atgttgggac  | ttgggaatcc  | cagcttttca  | gatccattta  | caggtggtgg  | 240  |
| tcggatagtt  | ccgggctctt  | cgggatcttc  | taacacacta  | cccacagcag  | atccttttac  | 300  |
| agggtcgtgt  | cggttatgtac | caggttctgc  | aagtatggga  | actaccatgg  | ccggagttga  | 360  |
| tccattttaca | gggaatagtg  | cctaccgatc  | agctgcattc  | aaaacaatga  | atattttatt  | 420  |
| ccctaaaaaa  | gaggctgtca  | catttgacca  | agcaaaccct  | acacaaatat  | taggttaaact | 480  |
| gaaggaaact  | aatggaactg  | cacctgaaga  | gaagaagtta  | actgaggatg  | acttgatact  | 540  |
| tcttgagaag  | atactgtctc  | taatatgtaa  | tagttcttca  | gaaaaaccca  | cagtccagca  | 600  |
| acttcagatt  | ttgtggaaag  | ctattaactg  | tcttgaagat  | attgtctttc  | ctgcacttga  | 660  |
| cattcttctcg | ttgtcaatta  | aacaccccag  | tgtgaatgag  | aacttctgca  | atgaaaagga  | 720  |
| aggggctcag  | ttcagcagtc  | atccttatcaa | tcttctgaac  | cctaaaggaa  | agccagcaaa  | 780  |
| ccagctgctt  | gctctcagga  | ctttttgcaa  | ttgttttggt  | ggccaggcag  | gacaaaaact  | 840  |
| catgatgtcc  | cagaggggaat | cactgatgtc  | ccatgcaata  | gaactgaaat  | cagggagcaa  | 900  |
| taagaacatt  | cacattgtct  | tggtacatt   | ggcctgaac   | tattctgttt  | gttttcataa  | 960  |
| agaccataac  | attgaaggga  | aagcccaatg  | ttgtcacta   | attagcacia  | tcttggaagt  | 1020 |
| agtacaagac  | ctagaagcca  | cttttagact  | tcttgtggct  | cttggaacac  | ttatcagtga  | 1080 |
| tgattcaaat  | gctgtacaat  | tagccaagtc  | tttaggtgtt  | gattctcaaa  | taaaaaagta  | 1140 |
| ttcctcagta  | tcagaaccag  | ctaaagtaag  | tgaatgctgt  | agatttatcc  | taaatttgct  | 1200 |
| gtagcagtgg  | ggaagaggga  | cggatatttt  | taattgatta  | gtgttttttt  | cctcacattt  | 1260 |
| gacatgactg  | ataacagata  | attaaaaaaa  | gagaatacgg  | tggattaaagt | aaaattttac  | 1320 |
| atcttgtaaa  | gtggtgggga  | ggggaaacag  | aaataaaaatt | tttgcactgc  | tgaaaaaaa   | 1380 |
| aaaaaaaaaa  | aaaaggaaac  | tcgagggggg  | gcccgg      |             |             | 1416 |

&lt;210&gt; 99

&lt;211&gt; 1760

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (255)

<223> n equals a,t,g, or c

<400> 99

|            |             |            |             |             |            |      |
|------------|-------------|------------|-------------|-------------|------------|------|
| gccttcaact | cttgttttat  | tganttatga | attcttaant  | cttctatggc  | aggagacatc | 60   |
| tatggggagg | ctttgtttgt  | tttttgagac | aggggtctcat | ttgtcgccca  | gggtgagact | 120  |
| ctgtctcaaa | aaaataaaat  | aaaataaaat | aaaaacaaag  | aaaaaaaaat  | aaaatcttta | 180  |
| ggcattccca | gacacaaaga  | tctcagagac | agacaacaga  | gagcytccgt  | gttcatctgc | 240  |
| ccgaggctgt | ttgtncacag  | ttcccttaaa | agatgcctgg  | aaatgctccc  | aacaacaagg | 300  |
| gactcaagta | tggggctgag  | tttgttaaaa | aagcagctaa  | atgtgttttag | gaaacacacg | 360  |
| aagtgaacc  | agacagtgat  | ggcccatgta | caagacttgt  | gcttgaagct  | ttggtgtgcc | 420  |
| tccatggcca | atttttcagg  | caccaaacc  | cattcctgat  | taattattgt  | taaaaaagca | 480  |
| gctaaatgtg | tttaggaaac  | acacgaagtg | aaaccagaca  | gtgatggccc  | atgtacaaga | 540  |
| cttggtgctg | aagcttttgt  | gtgcctccat | ggccaatttt  | tcaggcacca  | aaaccatttc | 600  |
| ctgattaatt | attgatatac  | aatgcaaacc | aaactatgaa  | aacacagact  | ttttttcaga | 660  |
| agagggaat  | aaaggcacag  | aaacctgcca | aaatagatat  | ttttttccat  | aagaatagta | 720  |
| tgggtgatta | aaatagttta  | tcactagtaa | aacttgatc   | actagagcag  | acaatacaaa | 780  |
| ttagtttttt | aaaaaatgac  | attcactgaa | ttcttggtct  | gtgcattcaa  | tgtgaataat | 840  |
| catcaaaaat | atattacaat  | ttaaaggttg | taaggagctc  | tgtctgggat  | ttctgcagta | 900  |
| tattatttcg | gaggagaaga  | accaccataa | agtatgagct  | atccactgtt  | cctttttatg | 960  |
| tcattgtatg | taatcagtct  | atctccta   | gcaggctcac  | aaacttccac  | gggtgagatg | 1020 |
| ctaagtgact | tagtgacctt  | cacactcatt | aaaggcagcc  | ctgtccatca  | aactccatac | 1080 |
| ctagaaaagt | caataaaactg | tattacattt | taataaatat  | ktctgtgtac  | tttttgtttt | 1140 |
| ttgcttttaa | gctcagctta  | aattttgtca | aggaaaccat  | ttcacaagac  | agtatgtcac | 1200 |
| agcctactat | cagcaatagt  | ccttgtttat | tagaatctgc  | agatgtccat  | attacatcaa | 1260 |
| atataaatat | atattatatt  | tacatttcct | tcttagcttt  | caatttaggt  | gagtgtattt | 1320 |
| atagataatg | ccactaacgc  | accactattc | taatcctcag  | tgcaactcat  | accttctttc | 1380 |
| cattagatgc | tcattaatgt  | aagacagcat | cttaaaagag  | gggtactgtt  | cttttttaaa | 1440 |
| ataaaaggaa | agaaaggga   | tccaagaatg | gaggtctaga  | catttcctaa  | gagatttttg | 1500 |
| ttttgttttt | tatacttaga  | aatacttgaa | aatgtggtc   | cctttttgta  | gtactagtct | 1560 |
| ctacttgggg | acaagaaaat  | agaatatgca | actcagaaag  | gaaagasccc  | aaagamgara | 1620 |
| raacctgctt | gtttactcca  | ttaacctgtt | taattaagat  | ctgcttttaa  | atgcctgatg | 1680 |
| ctgtgccagt | atcatacaaa  | acatcttcca | ccttccaagc  | agctgaagca  | cctcctcaaa | 1740 |
| attctgtttg | tcctgaataa  |            |             |             |            | 1760 |

<210> 100

<211> 599

<212> DNA

<213> Homo sapiens

<400> 100

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gaattcggca | cgagcgtcca | cgcagccgcc | ggccggccag | caccagggc  | cctgcatgcc | 60  |
| aggtcggttg | aggtggcagc | gagacatgca | cccggcccg  | aagctcctca | gcctcctctt | 120 |

|             |             |            |            |            |            |     |
|-------------|-------------|------------|------------|------------|------------|-----|
| cctcatcctg  | atggggcactg | aactcactca | agactccgct | gcccccgact | ccctgctgag | 180 |
| aagttcaaag  | ggcagcacga  | gggggtcttt | ggctgctatt | gtcatctgga | gggggaagag | 240 |
| tgagagccgg  | atagccaaga  | ccccaggcat | tttcagagg  | ggcgggacct | tagtcctacc | 300 |
| cccaacacac  | acccttgagt  | ggctcatcct | ccctttgggc | ataacgctgc | ccttgggggc | 360 |
| tccagaaaca  | ggcggtgagg  | attgtgccgc | tgagacctgg | aagggcagcc | agcgtgccgg | 420 |
| ccagctgtgt  | gcattgctgg  | cttaatatgc | agggcttggg | gggctgtggc | cacatgcccg | 480 |
| gcaggagggtg | agtgaggagc  | cctgtggcgt | gctgggtgtg | ggatcgtggg | catttcaaac | 540 |
| gggcttgtcg  | taccctgaac  | aatgtatcaa | tagagaaaaa | aaaaaaaaaa | aaaactcga  | 599 |

&lt;210&gt; 101

&lt;211&gt; 784

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 101

|             |             |            |             |             |             |     |
|-------------|-------------|------------|-------------|-------------|-------------|-----|
| gaattcggca  | cagaaaaaaa  | agagagactg | ggtcttactg  | tgttgcccag  | acttgtcttg  | 60  |
| aactcctgcc  | tcagcctctc  | aagtacttgg | gattataggg  | caagaagcca  | ccatgcctag  | 120 |
| cttcttccctg | tcattgatcc  | agactaatac | tctgggggtca | gcctcatttc  | ttctctttct  | 180 |
| cactttgcac  | atccacttgt  | caccaaack  | rgttcattct  | gcacctaag   | taagtccttt  | 240 |
| gattcctcca  | gttggtcatt  | agtaatgtct | caartgtaat  | tttttctagt  | agttttcagc  | 300 |
| ctgtctttcc  | kgccttcagt  | cttaacttct | ccagtacata  | kgccacattg  | ttgtcagcak  | 360 |
| gatcawattt  | tatttaaaaa  | tactttacaw | akgtttatkg  | ccaaatatta  | graaatacag  | 420 |
| attcatggaa  | agaaaaatca  | ctgtcccaag | gaggtcactg  | gcattggtgag | gttaaggggt  | 480 |
| gatttttaatt | tttaaaaatg  | tatatTTTTT | cctgtgtaga  | gtagtaaacac | ccttgaaaaac | 540 |
| acawtccctt  | gtaaaagtctc | taattctgta | ctccgcatct  | agstgrtctc  | ttctttctca  | 600 |
| gatatttttac | aatttcattt  | atcaccacct | ttctctagcc  | tttaccgctc  | tcttcaatat  | 660 |
| twacatatgc  | agaagtttct  | cctaacaac  | acctgcctct  | gcctcagttc  | tgtaccacc   | 720 |
| ctgttgcttt  | ctttcccttc  | acaatcaaat | ttaagagtgt  | caaaaaaaaa  | aaaaaaaaaac | 780 |
| tcga        |             |            |             |             |             | 784 |

&lt;210&gt; 102

&lt;211&gt; 404

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 102

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| ggcagcaggt | ataaaattga  | gactgatgaa | acatcaatac | tagagcccat | gaggatgaaa | 60  |
| gaaattatca | aatagtgtctg | aacagaataa | gatgttaacg | ctgagttatt | aggactggaa | 120 |
| ggctatgaaa | agaacttgaa  | attgtcggaa | tatgtgtctc | cttcatgtca | tattcaatag | 180 |
| aagtttctag | tttaagattg  | atTTTgtgtt | ttcttaggca | tttcaagtga | caagcaaagt | 240 |
| aaatgtatat | attatgtgat  | aaatcatgtt | ttcaagaacg | tcaaatttct | ggactttttt | 300 |
| ctttcaattt | ttaattttta  | aagttttttt | ggtattaaaa | aatctattca | caagccaaaa | 360 |
| aatatataaa | atatacagcg  | aaaagccaaa | aaaaaaaaaa | aaaa       |            | 404 |

&lt;210&gt; 103

&lt;211&gt; 760

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (438)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (741)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 103

|            |            |            |             |             |             |     |
|------------|------------|------------|-------------|-------------|-------------|-----|
| gggtcgaccc | acgcgtccgc | tgaccagtcc | gttatagata  | cttcttccta  | tacaaaaact  | 60  |
| gtttaaacag | gtgccaccac | aagggatgtc | gtccttactc  | tctgcgggtc  | ttcaagcatc  | 120 |
| cctttgtggg | aaargtctct | gggcaagcac | gtgggtatgtg | gtctgctgct  | tgcttccctt  | 180 |
| tttccaccag | ggatgttgtg | atcataagtc | aaaacaacag  | tatattccaa  | atctcaaaag  | 240 |
| ctattgtggc | ctgagcacia | ttgaaatcta | gcagagtttt  | tcctatgtag  | ctttagagta  | 300 |
| actcttctgc | ttctctgtca | cttacaattc | aggttctgcc  | tttgccctaag | agcatgagca  | 360 |
| gaagagtcct | catgtgacgc | ttagttctat | tgcagtcctg  | ggtgaaacta  | tttaagcwat  | 420 |
| ggggctgctk | ctcccanwt  | cctccctaac | aattcggtgt  | gtggacttct  | catctaaaag  | 480 |
| gtagtggtct | tttgcttggg | atcagtgtc  | tctattgatg  | ttcttgctgg  | tctccagaca  | 540 |
| cattcctgtt | gcattaagac | ttgaaagact | tgtagatgtg  | tgatgttcag  | gcacaggatg  | 600 |
| ctgaaagcta | tgttactatt | cttagtttgt | aaattgtcct  | tttgatacca  | tcattcttgtt | 660 |
| ttctttttgt | aggtataaat | aaaaacactg | ttgacaataa  | aaaaaaaaaa  | aaaaaaaaaa  | 720 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa  |             |             | 760 |

&lt;210&gt; 104

&lt;211&gt; 1351

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (544)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (774)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 104

|             |             |            |             |              |             |      |
|-------------|-------------|------------|-------------|--------------|-------------|------|
| cttcacagac  | tgacagaatg  | gttttgtttt | gttttgtttt  | gttttgtttt   | gtttttgaga  | 60   |
| tggactctag  | ctctgtcacc  | caggctggag | tgcagtgggtg | cgatctcggc   | tcactgcaag  | 120  |
| ctccgcctcc  | cgggttctca  | ccattctcct | gcctcagcct  | cccagtagc    | tgggactaca  | 180  |
| ggcgccacc   | accacgccc   | gctaattttt | tgtatttttt  | agtagagacg   | gggtttcacc  | 240  |
| atgttagcca  | ggatgggtctc | gatctcctga | cctcgtgac   | cgcccgcytc   | ggcctcccaa  | 300  |
| agtgtggga   | ttacaggcgt  | gagccaccgt | gcctgcccc   | gaatgggttt   | taaagccaca  | 360  |
| gttgagargc  | cacccattgc  | ccggcgctg  | gacagtgate  | atcttgttca   | tcttgttcag  | 420  |
| tcctttcttg  | tgtgattgga  | attattcatt | ccctttgaaa  | gatgagaagg   | ttgagatgca  | 480  |
| aagagtctac  | ctttccaagt  | tctcactgct | ggaagagact  | agaagcacag   | ttcaaagttc  | 540  |
| tggnttctgg  | actctgcagt  | ccaggtytcc | cttytcccac  | ttgcctaccc   | tcaatgccac  | 600  |
| actgtttttg  | aagtggccca  | taacttgaag | graaagttaa  | aagacagttc   | aatttaataca | 660  |
| tcagratgca  | ttcttttttt  | tttcggarac | ggaktttcac  | tcttgctgcc   | casgctggag  | 720  |
| tgcaatgggtg | caatgatctc  | ggctcactgc | aacctatgcc  | tcctgggttc   | aagngattat  | 780  |
| ccagcctcag  | cctcccgagt  | agctgggatt | atgggcgccc  | accaccatgc   | ccagctaatt  | 840  |
| tttgattttt  | tttttttagt  | agagatgggg | tttcgccagg  | ttggccaggc   | tgktcttggtg | 900  |
| aatctctggc  | ytccaggtgat | ytgcccacyt | catcytccaa  | aagtgtctggg  | attacaggca  | 960  |
| tgagccactg  | cgcctggcyt  | cagaatgcat | tcttacacat  | ctatcctaga   | catttataag  | 1020 |
| cactctaagt  | gataacaatc  | caagaataaa | tgattgtaaa  | agatgatgcc   | gaagagttga  | 1080 |
| tgtcaatctt  | tttttcctaa  | gaaaaaaagt | ccgcgagtat  | ttaaataattta | gatcaatggt  | 1140 |
| tataaaatga  | ttactttgta  | tatctcatta | ttcctatttt  | ggaataaaaa   | ctgaccttct  | 1200 |
| ttaatcatat  | acttgtcttt  | tgtaaatagc | agctttttgtg | tcattctccc   | cactttatta  | 1260 |
| gttaatttaa  | attggaaaaa  | accctcaaac | taatatctct  | gtctgttcca   | gtcttataaa  | 1320 |

taaaacttat aatgcatgta aaaaaaaaaa a

1351

<210> 105

<211> 2066

<212> DNA

<213> Homo sapiens

<400> 105

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ggcacgagggc | ggcgggagggc | cacaatcaca  | gctccggggca | ttgggggaac  | ccgagccggc  | 60   |
| tgcgccggggg | gaatccgtgc  | gggcgccttc  | cgtcccggtc  | ccatcctcgc  | cgcgctccag  | 120  |
| cacctctgaa  | gttttgagc   | gcccagaaag  | gaggcgagga  | aggagggagt  | gtgtgagagg  | 180  |
| agggagcaaa  | aagctcacc   | taaaacattt  | atttcaagga  | gaaaagaaaa  | agggggggcg  | 240  |
| caaaaatggc  | tggggcaatt  | atagaaaaca  | tgagcaccaa  | gaagctgtgc  | attgttgggtg | 300  |
| ggattctgct  | cgtgttccaa  | atcatcgcct  | ttctgggtggg | aggcttgatt  | gctccagggc  | 360  |
| ccacaacggc  | agtgtcctac  | atgtcgggtga | aatgtgtgga  | tgcccgttaag | aaccatcaca  | 420  |
| agacaaaatg  | gttcgtgcct  | tggggaccga  | atcattgtga  | caagatccga  | gacattgaag  | 480  |
| aggcaattcc  | aagggaatt   | gaagccaatg  | acatcgtgtt  | ttctgttcac  | attcccctcc  | 540  |
| cccacatgga  | gatgagtcct  | tggttccaat  | tcattgtgtt  | tatcctgcag  | ctggacattg  | 600  |
| ccttcaagct  | aaacaaccaa  | atcagagaaa  | atgcagaagt  | ctccatggac  | gtttccctgg  | 660  |
| cttaccgtga  | tgacgcattt  | gctgagtggg  | ctgaaatggc  | ccatgaaaga  | gtaccacgga  | 720  |
| aactcaaattg | caccttcaca  | tctcccaaga  | ctccagagca  | tgagggcgt   | tactatgaat  | 780  |
| gtgatgtcct  | tcctttcatg  | gaaattgggt  | ctgtggccca  | taagttttac  | cttttaaaca  | 840  |
| tccggctgcc  | tgtgaatgag  | aagaagaaaa  | tcaatgtggg  | aattggggag  | ataaaggata  | 900  |
| tccggttggg  | ggggatccac  | caaaatggag  | gcttcaccaa  | ggtgtgggtt  | gccatgaaga  | 960  |
| ccttccttac  | gcccagcatc  | ttcatcatta  | tggtgtggta  | ttggaggagg  | atcaccatga  | 1020 |
| tgtcccgacc  | cccagtgcct  | ctggaaaaag  | tcacttttgc  | ccttgggatt  | tccatgacct  | 1080 |
| ttatcaatat  | cccagtggaa  | tggttttcca  | tcgggtttga  | ctggacctgg  | atgctgctgt  | 1140 |
| ttggtgacat  | ccgacagggc  | atcttctatg  | cgatgcttct  | gtccttctgg  | atcatcttct  | 1200 |
| gtggcgagca  | catgatggat  | cagcacgagc  | ggaaccacat  | tgacagggtat | tggaagcaag  | 1260 |
| tcggaccat   | tgccgttggc  | tccttctgcc  | tcttcatatt  | tgacatgtgt  | gagagagggg  | 1320 |
| tacaactcac  | gaatcccttc  | tacagtatct  | ggactacaga  | cattggaaca  | gagctggcca  | 1380 |
| tggccttcac  | catcgtggct  | ggaatctgcc  | tctgcctcta  | cttctgtttt  | ctatgcttca  | 1440 |
| tggtatttca  | ggtgtttcgg  | aacatcagtg  | ggaagcagtc  | cagcctgcca  | gctatgagca  | 1500 |
| aagtcgggag  | gctacactat  | gaggggctaa  | tttttaggtt  | caagttcctc  | atgcttatca  | 1560 |
| ccttggcctg  | cgctgccatg  | actgtcatct  | tcttcatcgt  | tagtcaggta  | acggaaggcc  | 1620 |
| attggaaatg  | gggcggcgctc | acagtccaag  | tgaacagtg   | ctttttcaca  | ggcatctatg  | 1680 |
| ggatgtggaa  | tctgtatgtc  | tttgcctga   | tggtcttgta  | tgacacatcc  | cataaaaact  | 1740 |
| atggagaaga  | ccagtcctaat | ggaatgcaac  | tcccatgtaa  | atcgagggaa  | gattgtgctt  | 1800 |
| tgtttgtttc  | ggaactttat  | caagaattgt  | tcagcgcttc  | gaaatattcc  | ttcatcaatg  | 1860 |
| acaacgcagc  | ttctggtatt  | tgagtcaaca  | aggcaacaca  | tgtttatcag  | ctttgcattt  | 1920 |
| gcagttgtca  | cagtcacatt  | gattgtactt  | gtatacgcac  | acaaatacac  | tcatttagcc  | 1980 |
| tttatctcaa  | aatgtttaat  | ataaggaaaa  | aagcgtcaac  | aataaatatt  | cttgagtata  | 2040 |
| aaaaaaaaaa  | aaaaaaaaaa  | aaaaaa      |             |             |             | 2066 |

<210> 106

<211> 1705

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (724)

<223> n equals a,t,g, or c

<400> 106

aattcggcagc agggcagctg tcggctggaa ggaactgggc tgctcacact tgctggcttg

60

|            |             |             |             |             |             |      |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| cgcacagga  | ctggctttat  | ctcctgactc  | acggtgcaaa  | ggtgcactct  | gcgaacgtta  | 120  |
| agtcctccc  | cagcgcttgg  | aatcctacgg  | ccccacagc   | cggatcccct  | cagccttcca  | 180  |
| ggtcctcaac | tcccgyggac  | gctgaacaat  | ggcctccatg  | gggctacagg  | taatgggcat  | 240  |
| cgcgctggcc | gtcctgggct  | ggctggccgt  | catgctgtgc  | tgcgcgctgc  | ccatgtggcg  | 300  |
| cgtgacggcc | ttcatcggca  | gcaacattgt  | cacctcgag   | accatctggg  | agggcctatg  | 360  |
| gatgaactgc | gtgggtgcaga | gcaccggcca  | gatgcagtgc  | aagggtgtacg | actcgctgct  | 420  |
| ggcactgccc | caggacctgc  | aggcggcccc  | cgccctcgtc  | atcatcagca  | tcatcgctggc | 480  |
| tgtcttgggc | gtgctgctgt  | ccgtgggtggg | gggcaagtgt  | accaactgcc  | tggaggatga  | 540  |
| aagcgccaag | gccaagacca  | tgatcgtggc  | ggcggtgggtg | ttcctgttgg  | ccggccttat  | 600  |
| ggtgatagt  | cgggtgtcct  | ggacggccca  | caacatcatc  | caagacttct  | acaatccgct  | 660  |
| ggtggcctcc | gggcagaagc  | gggagatggg  | tgcctcgctc  | tacgtcggct  | gggcgcgctc  | 720  |
| cggmctgctg | ctccttggcg  | gggggctgct  | ttgctgcaac  | tgtccacccc  | gcacagacaa  | 780  |
| gccttactcc | gccaagtatt  | ctgctgccc   | ctctgctgct  | gccagcaact  | acgtgtaagg  | 840  |
| tgccacggct | ccactctgtt  | cctctctgct  | ttgttcttcc  | ctggactgag  | ctcagcgag   | 900  |
| gctgtgaccc | caggagggcc  | ctgccacggg  | ccactggctg  | ctggggactg  | gggactgggc  | 960  |
| agagactgag | ccaggcagga  | aggcagcagc  | cttcagcctc  | tctggcccac  | tcggacaact  | 1020 |
| tcccaaggcc | gcctcctgct  | agcaagaaca  | gagtcacccc  | tcctctggat  | attggggagg  | 1080 |
| gacggaagt  | acaggggtgtg | gtgggtggagt | ggggagctgg  | cttctgctgg  | ccaggatggc  | 1140 |
| ttaaccctga | ctttgggac   | tgcctgcatc  | gggtgtggcc  | actgtcccca  | tttacatttt  | 1200 |
| ccccactctg | tctgcctgca  | tctcctctgt  | tgcgggtagg  | ccttgatata  | acctctggga  | 1260 |
| ctgtgccttg | ctcaccgaaa  | cccgcgccca  | ggagtatggc  | tgaggccttg  | cccaccacc   | 1320 |
| tgcctgggaa | gtgcagagt   | gatggacggg  | tttagagggg  | aggggcgaag  | gtgctgtaaa  | 1380 |
| cagggttggg | cagtgggtggg | ggagggggcc  | agagaggcgg  | ctcaggttgc  | ccagctctgt  | 1440 |
| ggcctcagga | ctctctgcct  | caccgccttc  | agcccagggc  | ccctggagac  | tgatccctc   | 1500 |
| tgagtctct  | gccccctcca  | aggacactaa  | tgagcctggg  | aggggtggcag | ggaggagggg  | 1560 |
| acagcttcac | ccttggaagt  | cctgggggtt  | ttcctcttcc  | ttctttgtgg  | tttctgtttt  | 1620 |
| gtaatttaag | aagagctatt  | catcactgta  | attattatta  | ttttctacaa  | taaattgggac | 1680 |
| ctgtgcacag | graaaaaaaa  | aaaag       |             |             |             | 1705 |

&lt;210&gt; 107

&lt;211&gt; 1167

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 107

|            |            |            |             |            |             |     |
|------------|------------|------------|-------------|------------|-------------|-----|
| nggagntcca | cgcggtggc  | ggcgcctcta | gaactagtgg  | atcccccggg | ctgcaggaat  | 60  |
| tcggcacgag | gccaccaacc | gtggcatcac | gcgaatccgg  | ggcaccagct | accagagccc  | 120 |
| tcacggcatc | cccatagacc | tgttgacag  | gcgccatgtc  | actctccagg | gcccggttga  | 180 |
| ggaaggagaa | gctctcgatg | tccagcatgt | ggacctcgtc  | gatgaacagc | actccaggga  | 240 |
| tgatctccgc | cttgccctcc | tcgcgccact | cagccacctt  | ggcattgata | tgtcacgga   | 300 |
| cttctgactt | gatctcccct | gtgtcacctg | agaagagcgc  | caggaagccc | tgggtgcgag  | 360 |
| agttgatgac | gtcgatctcg | tgcagggaca | cgggtgtgcac | cacctccttg | cgtttctgga  | 420 |
| gctccccatc | tgggactgac | acgaacttgg | tctgggagcc  | catagcgctg | tagttcgagg  | 480 |
| gcgcgtgtga | aggagcggcc | cagcttggag | atcttgcccc  | tcgcttctgc | gatgggtgatc | 540 |
| acgtccccgg | cctggacctt | gtccttgggc | agggamtcaa  | tcacttctgt | gcccaggctcg | 600 |
| tagatgggtc | ccatctctgt | ggctcttgag | gtcagtttgc  | ccaccttgga | gcccgtccct  | 660 |
| gttgcctggc | gatcaatctg | gatctccacc | acctccccct  | cgatgatctc | cgtctcctcc  | 720 |

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| ttgatgcgaa | cgccgatgga | cgcgcggaag | gectgcgtca | gcgcctcgg  | cttgetcatc | 780  |
| tccagggaga | agattttact | gccggcgatg | gctgtgaatg | gcgtgtcagg | gcccagggcc | 840  |
| tgcgccatgc | ccatggcgat | ggccgtcttc | cccgtgccc  | gctggccagc | aataaggact | 900  |
| gcccagaccg | caatcttccc | ttcccggatc | atctccagca | ccacgccagc | cgcccgcgt  | 960  |
| gccgccagct | gacccaccat | gccttgcgaa | gcctgccgag | gctccaaggc | atcgtccagc | 1020 |
| cccagtcccc | ggatgtggga | gtgggcaccg | attcgtctca | tccttggtac | atcacggatc | 1080 |
| tccgggactt | tgggtgtggc | tgtaacgggt | gccatgatgc | tcaccaactg | ccagagtcta | 1140 |
| gcggaaaacc | tctgccgaat | tcctgca    |            |            |            | 1167 |

&lt;210&gt; 108

&lt;211&gt; 1907

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 108

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| ggcacagggg | aatcatcgtg | tgatgtgtgt | gctgcctttg | tgagtgtgtg | gagtcctgct | 60   |
| caggtgttag | gtacagtgtg | tttgatcgtg | gtggcttgag | gggaaccctt | gttcagagct | 120  |
| gtgactgcgg | ctgcactcag | agaagctgcc | cttggtctgt | cgtagcgccg | ggccttctct | 180  |
| cctcgtcatc | atccagagca | gccagtgtcc | gggaggcaga | aggtagccgg | gcagctactg | 240  |
| gaggactgtg | cgggcctgcc | tgggtgtccc | cctccgccgt | ggggccctgt | tgctgctgtc | 300  |
| catctatttc | tactactccc | tcccaaatgc | ggtcggcccg | cccttcaact | ggatgcttgc | 360  |
| cctcctgggc | ctctcgcagg | cactgaacat | cctcctgggc | ctcaagggcc | tggccccagc | 420  |
| tgagatctct | gcagtgtgtg | aaaaaggga  | tttcaacgtg | gcccattggc | tggcatggtc | 480  |
| atattacatc | ggatatctgc | ggctgatcct | gccagagctc | caggcccggg | ttcgaactta | 540  |
| caatcagcat | tacaacaacc | tgctacgggg | tgcatgtgag | cagcggctgt | atattctcct | 600  |
| cccattggac | tgtggggtgc | ctgataacct | gagtaggtgt | gacccaaca  | ttcgtctcct | 660  |
| ggataaactg | ccccagcaga | cgggtgaccg | tgctggcatc | aaggatcggg | tttacagcaa | 720  |
| cagcatctat | gagcttcttg | agaacgggca | gcggggcgcc | acctgtgtcc | tggagtacgc | 780  |
| cacccccctg | cagactttgt | ttgccatgtc | acaatacagt | caagctggct | ttagcgggga | 840  |
| ggataggctt | gagcaggcca | aactcttctg | ccggacactt | gaggacatcc | tggcagatgc | 900  |
| ccctgagtct | cagaacaact | gccgcctcat | tgctaccag  | gaacctgcag | atgacagcag | 960  |
| cttctcgctg | tcccaggagg | ttctccggca | cctgcggcag | gaggaaaagg | aagaggttac | 1020 |
| tgtgggcagc | ttgaagacct | cagcgggtgc | cagtacctcc | acgatgtccc | aagagcctga | 1080 |
| gctcctcatc | agtggaatgg | aaaagcccct | ccctctccgc | acggatttct | cttgagacct | 1140 |
| agggtcacca | ggccagagcc | tccagtggtc | tccaagcctc | tggactgggg | gctctcttca | 1200 |
| gtggctgaat | gtccagcaga | gctatttctt | tccacagggg | gccttgccag | gaagggtcca | 1260 |
| ggacttgaca | tcttaagatg | cgtcttgtcc | ccttgggcca | gtcatttccc | ctctctgagc | 1320 |
| ctcgggtgtc | tcaacctgtg | aaatgggatc | ataatcactg | ccttacctcc | ctcacgggtg | 1380 |
| ttgtgaggac | tgagtgtgtg | gaagtttttc | ataaactttg | gatgctagtg | tacttagggg | 1440 |
| gtgtgccagg | tgtctttcat | ggggccttcc | agacccactc | cccacccttc | tccccttctt | 1500 |
| ttgcccgggg | acgccgaact | ctctcaatgg | tatcaacagg | ctccttcgcc | ctctggctcc | 1560 |
| tggtcatgtt | ccattattgg | ggagcccag  | cagaagaatg | gagaggagga | ggaggctgag | 1620 |
| tttgggggat | tgaatcccc  | ggctcccacc | ctgcagcatc | aagggtgcta | tggactctcc | 1680 |
| tgcggggcaa | ctcttgcgta | atcatgacta | tctctaggat | tctggcacca | cttcttccc  | 1740 |
| tggcccctta | agcctagctg | tgtatcggca | ccccaccccc | actagagtac | tccctctcac | 1800 |
| ttgcgggttc | cttatactcc | acccctttct | caacggtcct | tttttaaagc | acatctcaga | 1860 |
| ttaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaag | cgccgcgc   |            | 1907 |

&lt;210&gt; 109

&lt;211&gt; 611

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

<223> n equals a,t,g, or c.

<220>

<221> SITE

<222> (21)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (47)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (607)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (610)

<223> n equals a,t,g, or c

<400> 109

|             |             |            |            |            |             |     |
|-------------|-------------|------------|------------|------------|-------------|-----|
| atgaattaac  | gccaagctnt  | naatagggac | tcactatggg | ggaaagntgg | gtaacgcctg  | 60  |
| caggtaaccgt | tccggaattc  | cggggtcgac | ccacgcgtcc | gatggggctt | tagtaaataca | 120 |
| ggcttgacagg | ctcaaagctg  | caatctgccc | actctcaggt | actgagactt | tgtgggcctc  | 180 |
| agacaccagg  | aagaaagttg  | ggatacagtc | atttgagtta | aaaagggaat | gacccctcag  | 240 |
| aaacccgcac  | tagcagtgtt  | actcttgga  | gtgcctttac | ttttaacgct | ctctgttctg  | 300 |
| aaaaagaggt  | gtttgggttac | gtgtgagcca | acatcacgtt | ttgttagctg | tgatttacct  | 360 |
| ttgtccgttt  | aaaagacttc  | acggagccat | tctgtataca | aggtgtgctc | tttccaatgt  | 420 |
| agaaggggtt  | atggaaaagg  | gtgcgatcct | ttgctgtaaa | ctggagagac | cagtcccaaa  | 480 |
| cagaggggaa  | ttttaagccc  | ttctcatcac | ccaattggat | gtttttgctt | atagcaaatt  | 540 |
| cctgcaaaat  | aaataaataa  | atatttgcaa | aactaaaaaa | aaaaaaaaaa | aaaaaaaaaa  | 600 |
| gggggggnccn | c           |            |            |            |             | 611 |

<210> 110

<211> 2632

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2620)

<223> n equals a,t,g, or c

<400> 110

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| tcccagctct | caggacaagg | gccctgggcg | atctttttaa | aaagccgatt | gggtgtcttt | 60  |
| ctaaaantac | aaccagtact | tcacgtgcaa | gtttctggga | agggagtccc | ctccagattc | 120 |
| tcattggagt | acaaatcttg | actcttgctc | ctggaatttt | tcaggcccaa | actagcgttt | 180 |
| ctacaatgat | ttatttggca | aatttgtctt | gattatgggt | ggctgatgag | gaacgtgctt | 240 |
| ttgttaggaa | ccgaaactgg | gcggcggtga | ggcgtgtac  | gcaatgagtc | cggagagagg | 300 |
| tgaaatgctt | tcggtaggca | ctccacggct | gtgaagatgg | cggcggtgc  | gtggcttcag | 360 |



|             |             |            |             |            |             |      |
|-------------|-------------|------------|-------------|------------|-------------|------|
| gtgttgccctg | tcattctctct | gcttctggga | gctcaccctg  | caccactgtc | gtttttcagt  | 420  |
| gcgggaccgg  | caaccgtagc  | tgctgccgac | cgggtccaaat | ggcacattcc | gataccgtcg  | 480  |
| gggaaaaaatt | attttagttt  | tggaaagatc | ctcttcagaa  | ataccactat | cttcctgaag  | 540  |
| tttgatggag  | aaccttgtag  | cctgtctttg | aatataacct  | ggtatctgaa | aagcgctgat  | 600  |
| tgttacaatg  | aaatctataa  | cttcaaggca | gaagaagtag  | agttgtattt | ggaaaaactt  | 660  |
| aaggaaaaaaa | gaggcttgct  | tgggaaatat | caaacatcat  | caaaattgtt | ccagaactgc  | 720  |
| agtgaactct  | ttaaaacaca  | gaccttttct | ggagatttta  | tgcacgcact | gcctctttta  | 780  |
| ggagaaaaaac | aggaggctaa  | ggagaatgga | acaaacctta  | cctttattgg | agacaaaacc  | 840  |
| gcaatgcatg  | aaccattgca  | aacttgcaa  | gatgcaccat  | acatttttat | tgtacatatt  | 900  |
| ggcatttcat  | cctcaaagga  | atcatcaaaa | gaaaattcac  | tgagtaatct | ttttaccatg  | 960  |
| actggtgaag  | tgaagggctc  | ctatgaatac | ctcacacttg  | aagactatcc | cttgatgatt  | 1020 |
| tttttcatgg  | tgatgtgtat  | tgtatatgtc | ctgtttgggt  | ttctgtgggt | ggcatggctc  | 1080 |
| gcctgctact  | ggagagatct  | cctgagaatt | cagttttgga  | ttgggtgctg | catcttcctg  | 1140 |
| ggaatgcttg  | agaaagctgt  | cttctatgcg | gaatttcaga  | atatccgata | caaaggaraa  | 1200 |
| tctgtccagg  | gtgctttgat  | ccttgcagar | ctgctttcag  | cagtgaacag | ctcactggct  | 1260 |
| cgaaccctgg  | tcatcatagt  | cagtctggga | tatggcatcg  | tcaagccacg | cctggagtca  | 1320 |
| ctcttcataa  | ggttgtagta  | gcagragccc | tctatctttt  | gttctctggc | atggaagggg  | 1380 |
| tcctcagagt  | tactggggcc  | cagactgatc | ttgcttcctt  | ggcctttatc | cccttggett  | 1440 |
| tcctagacac  | tgccttgtag  | tggtggatat | ttattgcct   | gactcaaaca | atgaagctat  | 1500 |
| taaaacttcg  | gaggaacatt  | gtaaaactct | ctttgtatcg  | gcatttcacc | aacacgctta  | 1560 |
| ttttggcagt  | ggcagcatcc  | attgtgttta | tcatctggac  | aaccatgaag | ttcagaatag  | 1620 |
| tgacatgtca  | gtcggactgg  | cgggagctgt | gggtagacga  | tgccatctgg | cgcttgctgt  | 1680 |
| tctccatgat  | cctctttgtc  | atcatgggtc | tctggcgacc  | atctgcaaac | aaccagaggt  | 1740 |
| ttgccttttc  | accattgtct  | gaggaagagg | aggaggatga  | acaaaaggag | cctatgctga  | 1800 |
| aagaaagctt  | tgaaggaatg  | aaaatgagaa | gtaccaaaca  | agaaccaaat | ggaaatagta  | 1860 |
| aagttaacaa  | agcacaggaa  | gatgatttga | agtgggtaga  | agagaatgtt | ccttctctctg | 1920 |
| tgacagatgt  | agcacttcca  | gcccttctgg | attcagatga  | ggaacgaatg | atcacacact  | 1980 |
| ttgaaagggtc | caaaatggag  | taaggaatgg | gaagatttgc  | agttaaagat | ggctaccatc  | 2040 |
| agggaagaga  | tcagcatctg  | tgtcagtctt | ctgtacggct  | ccatgggatt | aaaggaagca  | 2100 |
| atgacatcct  | gatctgttcc  | ttgatctttg | ggcattggag  | ttggcgagag | gtgtcagaac  | 2160 |
| aaagagaaca  | tcttactgaa  | aacaagttca | taagatgaga  | aaaatctacg | agcttcttat  | 2220 |
| ttacaacact  | gctgccccct  | ttcctcccag | actctgacat  | ggatgttcat | gcaacttaag  | 2280 |
| tgtgtgttgc  | ctgaactttc  | tgtaatgttt | cattttttta  | atctgacaaa | ctaaaaagtt  | 2340 |
| taacgtcttc  | taaaagattg  | tcatcaacac | cataatatgt  | aatctccagg | agcaactgcc  | 2400 |
| tgtaattttt  | atatttttag  | ggagttacat | agggtgatgg  | ggaaattgtt | aactaccttt  | 2460 |
| cattttcctg  | ggaagtcaag  | gttacatctt | gcagaggttg  | ttttgagaaa | aaagggccct  | 2520 |
| tctgagttaa  | ggagccatag  | ttctatcaat | gatcaaaaaga | aaaaaaaaaa | aactcgatcg  | 2580 |
| gcacgagggg  | gggcccggta  | cccaattcgc | cctatgggan  | tcgaatgaga | cc          | 2632 |

&lt;210&gt; 111

&lt;211&gt; 2249

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1579)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2226)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 111

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gaattcggca | cgagctcacc | gtgctgcgtg | acacaaggcc | agcctgcgcc | tacgagccca | 60  |
| tggactttkt | ratggccctc | atctacgaca | tggtactgsw | tgtggtcacc | ctggggctgg | 120 |

|            |             |            |            |            |             |      |
|------------|-------------|------------|------------|------------|-------------|------|
| ccctcttcac | tctgtgcggc  | aagttcaaga | ggtggaagct | gaacggggcc | ttcctctca   | 180  |
| tcacagcctt | cctctctgtg  | ctcatctggg | tggcctggat | gaccatgtac | ctcttcggca  | 240  |
| atgtcaagct | gcagcagggg  | gatgcctgga | acgacccac  | cttggccatc | acgctggcgg  | 300  |
| ccagcgtctg | gtcttcgtca  | tcttcacgc  | catccctgag | atccactgca | cccttctgcc  | 360  |
| agccctgcag | gagaacacgc  | ccaactactt | cgacacgtcg | cagcccagga | tgcgggagac  | 420  |
| ggccttcgag | gaggacgtgc  | agctgccgcg | ggcctatatg | gagaacaagg | ccttctccat  | 480  |
| ggatgaacac | aatgcagctc  | tccgaacagc | aggatttccc | aacggcagct | tgggaaaaag  | 540  |
| acccagtggc | agcttgggga  | aaagaccag  | cgctccgttt | agaagcaacg | tgtatcagcc  | 600  |
| aactgagatg | gccgtcgtgc  | tcaacggtgg | gaccatccca | actgctccgc | caagtccac   | 660  |
| aggaagamac | ctttggtgaa  | agactttaag | ttccagagaa | tcagaatttc | tcttaccgat  | 720  |
| ttgcctccct | ggctgtgtct  | ttcttgaggg | agaaatcggt | aacagttgcc | gaaccaggcc  | 780  |
| gcctcacagc | caggaaattt  | ggaaatccta | gccaagggga | tttcgtgtaa | atgtgaacac  | 840  |
| tgacgaactg | aaaagctaac  | accgactgcc | cgccccctcc | ctgccacaca | cacagacag   | 900  |
| taataccaga | ccaacctcaa  | tccccgcaa  | ctaaagcaaa | gctaattgca | aatagtatta  | 960  |
| ggctcactgg | aaaatgtggc  | tgggaagact | gtttcatcct | ctgggggtag | aacagaacca  | 1020 |
| aattcacagc | tgggtggcca  | gactggtgtt | ggttggaggt | ggggggctcc | cactcttatc  | 1080 |
| acctctcccc | agcaagtgtc  | ggaccccagg | tagcctcttg | gagatgaccg | ttgcgttgag  | 1140 |
| gacaaatggg | gactttgcca  | cggctttgc  | ctggtggttt | gcacatttca | ggggggctag  | 1200 |
| gagagttaag | gaggttgttg  | gtggattcc  | aaggtgaggc | ccaactgaat | cgtgggggtga | 1260 |
| gctttatagc | cagtagaggt  | ggagggaccc | tggcatgtgc | caaagaagag | gccctctggg  | 1320 |
| tgatgaagtg | accatcacat  | ttggaaagtg | atcaaccact | gttccttcta | tggggctctt  | 1380 |
| gctctagtgt | ctatggtgag  | aacacaggcc | ccgccccttc | ccttgtagag | ccatagaaat  | 1440 |
| attctggctt | ggggcagcag  | tccctctctc | ccttgatcat | ctcgccctgt | tcctacactt  | 1500 |
| acgggtgtat | ctccaaatcc  | tctcccaatt | ttattccctt | attcatttca | agagctccaa  | 1560 |
| tggggtctcc | tgatgtcacc  | tagcagggct | tcagggggtc | ccactaggat | gcagagatga  | 1620 |
| ttttccgcga | cctcacaaagc | agtgacacct | cgggtccttt | ccgttgctat | ggtgaaaatt  | 1680 |
| cctctcgctg | cctcacaaagc | agtgacacct | cgggtccttt | ccgttgctat | ggtgaaaatt  | 1740 |
| cctggatgga | atggatcaca  | tgagggtttc | ttgttgcttt | tggagggtgt | gggggatatt  | 1800 |
| ttgttttggt | ttttctgcag  | gttccatgaa | aacagccctt | ttccaagccc | attgtttctg  | 1860 |
| tcatggtttc | catctgtcct  | gagcaagtca | ttcctttgtt | atttagcatt | tcgaacatct  | 1920 |
| cggccattca | aagcccccat  | gttctctgca | ctgtttggcc | agcataacct | ctagcatcga  | 1980 |
| ttcaaagcag | agttttaacc  | tgacggcatg | gaatgtataa | atgagggtgg | gtccttctgc  | 2040 |
| agatactcta | atcactacat  | tgctttttct | ataaaactac | ccataagcct | ttaaccttta  | 2100 |
| aagaaaaatg | aaaaaggtta  | gtgtttgggg | gccgggggag | gactgaccgc | ttcataagcc  | 2160 |
| agtacgtctg | agctgagtat  | gtttcaataa | accttttgat | atttctcaaa | aaaaaaaaaa  | 2220 |
| aaaaancccc | ggggggggcc  | cggacctgg  |            |            |             | 2249 |

&lt;210&gt; 112

&lt;211&gt; 2198

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (123)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (621)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (640)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 112

|             |             |            |             |            |             |      |
|-------------|-------------|------------|-------------|------------|-------------|------|
| gatactataa  | ggcaagtgc   | tcacgggtgc | gccgttagac  | tagtggatcc | cgggtgcagg  | 60   |
| aattcggcag  | agcgcgcgcg  | gagccgaagt | gctggcgccc  | ccgcggccgc | tgcctccgcg  | 120  |
| gancccaaaa  | tcatgaaagt  | caccgtgaag | accccgaa    | aaaggaggaa | ttcgccgtgc  | 180  |
| ccgagaatag  | ctccgtccag  | cagtttaagg | aagaaatctc  | taaacgtttt | aaatcacata  | 240  |
| ctgaccaact  | tgtgttgata  | tttgctggaa | aaattttgaa  | agatcaagat | accttgagtc  | 300  |
| agcatggaat  | tcatgatgga  | cttactgttc | accttgtcat  | taaaacacaa | aacaggcctc  | 360  |
| aggatcattc  | agctcagcaa  | acaaatacac | ctggaagcaa  | tgttactaca | tcatcaactc  | 420  |
| ctaatagtaa  | ctctacatct  | ggttctgcta | ctagcaaccc  | ttttggttta | ggtggccttg  | 480  |
| ggggacttgc  | aggtctgagt  | agcttgggtt | tgaatactac  | caacttctct | gaactacaga  | 540  |
| gtcagatgca  | gcgacaactt  | ttgtctaacc | ctgaaaatgat | ggtccagatc | atggaaaaawc | 600  |
| ccyttgttca  | gagcatgtct  | ntcaaactct | gacctgatgn  | agacagttaa | ttatggccaa  | 660  |
| tccacaaatg  | cagcagttga  | tacagagaaa | tcccagaaat  | tagtcatatg | ttgaataatc  | 720  |
| cagatataat  | gagacaaacg  | ttggaacttg | cccaggaatc  | cagcaatgat | gcaggagatg  | 780  |
| atgaggaacc  | aggaccgagc  | tttgagcaac | ctagaaaagca | tcccaggggg | atataatgct  | 840  |
| ttaaggcgca  | tgtacacaga  | tattcaggaa | ccaatgctga  | gtgctgcaca | agagcagttt  | 900  |
| ggtggtaatc  | catttgcttc  | cttggtgagc | aatacatcct  | ctggtgaagg | tagtcaacct  | 960  |
| tcccgtagac  | aaaatagaga  | tccactaccc | aatccatggg  | ctccacagac | ttcccagagt  | 1020 |
| tcatcagctt  | ccagcggcac  | tgccagcact | gtgggtggca  | ctactggtag | tactgccagt  | 1080 |
| ggcacttctg  | ggcagagtac  | tactgcgcca | aatttggtgc  | ctggagtagg | agctagtatg  | 1140 |
| ttcaacacac  | caggaatgca  | gagcttgttg | caacaaataa  | ctgaaaaccc | acaacttatg  | 1200 |
| caaaacatgt  | tgtctgcccc  | ctacatgaga | agcatgatgc  | agtcactaag | ccagaatcct  | 1260 |
| gaccttgctg  | cacagatgat  | gctgaataat | cccctatattg | ctggaaatcc | tcagcttcaa  | 1320 |
| gaacaaatga  | gacaacagct  | cccaactttc | ctccaacaaa  | tgcagaatcc | tgatacacta  | 1380 |
| tcagcaatgt  | caaaccctag  | agcaatgcag | gccttggttac | agattcagca | gggtttacag  | 1440 |
| acattagcaa  | cgggaagcccc | gggcctcatc | ccagggttta  | ctcctggctt | gggggcatta  | 1500 |
| ggaagcactg  | gaggctcttc  | gggaactaat | ggatctaacg  | ccacacctag | tgaaaacaca  | 1560 |
| agtcccacag  | caggaaccac  | tgaacctgga | catcagcagt  | ttattcagca | gatgctgcag  | 1620 |
| gctcttgctg  | gagtaaatcc  | tcagctacag | aatccagaag  | tcagatttca | gcaacaactg  | 1680 |
| gaacaactca  | gtgcaatggg  | atttttgaac | cgtgaagcaa  | acttgcaagc | tctaatagca  | 1740 |
| acaggagggtg | atatcaatgc  | agctattgaa | aggttactgg  | gctcccagcc | atcatagcag  | 1800 |
| catttctgta  | tctkgaaaaa  | atgtaattta | tttttgataa  | cggctcttaa | actttaaaat  | 1860 |
| acctgcttta  | tttcattttg  | actcttgtaa | ttctgtgctg  | ttataaacia | acccaatag   | 1920 |
| atgcatttta  | aggtggagta  | cagtaagatg | tgtgggtttt  | tctgtatttt | tcttttctgg  | 1980 |
| aacagtggga  | attaaggcta  | ctgcatgcat | cacttctgca  | tttattgtaa | ttttttaaaa  | 2040 |
| acatcacctt  | ttatagttgg  | gtgaccagat | tttgtcctgc  | atctgtccag | tttatttgct  | 2100 |
| ttttaaacat  | tagcctatgg  | tagtaattta | tgtagaataa  | aagcattaaa | aagaagcaaa  | 2160 |
| aaaaaaaaaa  | aaaaattcct  | gcgcccgcga | attcttct    |            |             | 2198 |

&lt;210&gt; 113

&lt;211&gt; 1043

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 113

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| ctgaagtgtg | tgtgggtgag | aagaagagge | tctactgtg  | gacagccttg | ttctacagat  | 60  |
| cctcccagaa | atctctgggc | caggtggaac | ccagggtcag | agagggatgg | gagagagggt  | 120 |
| taattttcca | tgataaataa | aaatctataa | aataataaac | aagagaaaag | agattggaaa  | 180 |
| cagccaggtt | ggagcagtga | gtgagtaagg | aaacctggct | gccctctcca | gattccccag  | 240 |
| gctctcagag | aagatcagca | gaaagtctgc | aagaccctaa | gaaccatcag | ccctcagctg  | 300 |
| cacctcctcc | cctccaagga | tgacaaaggc | gctactcctc | tatttggtca | gcagctttct  | 360 |
| tgccctaaat | caggccagcc | tcatcagtcg | ctgtgacttg | gcccaggtgc | tgagctgga   | 420 |
| rgacttggtg | gggtttgagg | gttactccct | gagtgcactg | ctgtgcctgg | cttttggtgga | 480 |
| aagcaagttc | aacatatcaa | agatwaatga | aaatgcagat | ggaagctttg | actatggsct  | 540 |
| cttcagatc  | aacagccact | actggtgcaa | crattataag | agttactcgg | aaaacctttg  | 600 |
| ccacgtagac | tgtcaagatc | tgctgaatcc | caaccttctt | gcaggcatcc | actgcgcaaa  | 660 |
| aaggattgtg | tccggagcac | gggggatgaa | caactgggtt | agaatggaag | kttgcactgt  | 720 |

|             |             |            |            |            |            |      |
|-------------|-------------|------------|------------|------------|------------|------|
| tcaggccggc  | caactcttcta | ctggctgaca | ggatgccgcc | tgagatkaaa | carggtgcgg | 780  |
| gtgcaccgtg  | gartcattcc  | aagactcctg | tcctcactca | rggattcttc | atttcttctt | 840  |
| cctactgcct  | ccacttcacg  | ttatcttctt | cccttcccat | ttacaactaa | aactgaccag | 900  |
| agccccagga  | ataaatgggt  | ttcttggctt | cctccttact | cccatctgga | cccagtcccc | 960  |
| tgggttcctgt | ctgttatttg  | taaactgagg | accacaataa | agaaatcttt | atatttatog | 1020 |
| aaaaaaaaaa  | aaaaaaaaact | cga        |            |            |            | 1043 |

&lt;210&gt; 114

&lt;211&gt; 703

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 114

|            |             |            |             |            |            |     |
|------------|-------------|------------|-------------|------------|------------|-----|
| gaattcggca | cgagtgcgcg  | ggcaccacgg | cggtttttctg | acgctggcgg | tggacgcagg | 60  |
| cagcatggac | cacggttgct  | gggoggatgg | ggagcgtcta  | tggtcagttg | ccttagaagt | 120 |
| ggtgagatgg | gaagctgcag  | ttggaagacc | ctggaggatg  | cctgacaagg | ggatgtctga | 180 |
| cacatgattg | gagctctttt  | tgaaatgttt | cttgcccttc  | ctggagcaga | ggagccatta | 240 |
| tttatgcagg | tacatcgaag  | tcttttgacc | tccatacagt  | gattatgctt | gtcatcgctg | 300 |
| gtggtatcct | ggcggccttg  | ctcctgctga | tagttgtcgt  | gctctgtctt | tacttcaaaa | 360 |
| tacacaacgc | gctaaaagct  | gcaaaggaac | ctgaagctgt  | ggctgtaaaa | aatcacaacc | 420 |
| cagacaaggt | gtggtgggccc | aagaacagcc | aggccaaaac  | cattgccacg | gagtcttgtc | 480 |
| ctgccctgca | gtgctgtgaa  | ggatatagaa | tgtgtgccag  | ttttgattcc | ctgccacctt | 540 |
| gctgttgcca | cataaatgag  | ggcctctgag | ttaggaaagg  | tgggcacaaa | aatcttcatg | 600 |
| agcaatactt | cttagtagat  | tgttttggtt | ttcaaataca  | gttctagtgt | ttttatgtga | 660 |
| gattatataa | tttacagtgt  | tgttttatat | acttttgaat  | aaa        |            | 703 |

&lt;210&gt; 115

&lt;211&gt; 3684

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (79)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2297)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3679)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 115

|            |            |            |             |             |             |     |
|------------|------------|------------|-------------|-------------|-------------|-----|
| ggcagagggg | gcatgagcag | gaggaggatt | accgctacga  | ggtgctcacg  | gccgagcaga  | 60  |
| ttctacaaca | catggtggna | atgtatccgg | gagggtcaacg | agggtcatcca | gaatccagca  | 120 |
| actatcacaa | gaatactcct | tagccacttc | aattggggata | aagagaagct  | aatggaaagg  | 180 |
| tactttgatg | gaaacctgga | gaagctcttt | gctgagtgtc  | atgtaattaa  | tccaagtaaa  | 240 |
| aagtctcgaa | cacgccagat | gaatacaagg | tcatacagcac | aggatatgcc  | ttgtcagatc  | 300 |
| tgctacttga | actaccctaa | ctcgtatttc | actggccttg  | aatgtggaca  | taagttttgt  | 360 |
| atgcagtgtc | ggagtgaata | tttaactacc | aaaataatgg  | aagaaggcat  | gggtcagact  | 420 |
| atttcgtgtc | ctgctcatgg | ttgtgatata | ttagtggatg  | acaacacagt  | tatgcgcctg  | 480 |
| atcacagatt | caaaagttaa | attaaagtat | cagcatttaa  | taacaaatag  | ctttgttagag | 540 |

|            |             |             |             |             |             |      |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| tgcaatcgac | tgtaaagt    | gtgtcctgcc  | ccagattgcc  | accatgttgt  | taaagtccaa  | 600  |
| tatcctgatg | ctaaacctgt  | tcgctgcaaa  | tgtgggcgcc  | aattttgctt  | taactgtgga  | 660  |
| gaaaattggc | atgatcctgt  | taaatgtaag  | tggttaaaga  | aatggattaa  | aaagtgtgat  | 720  |
| gatgacagt  | aaacctccaa  | ttggattgca  | gccaacacaa  | aggaatgtcc  | caaatgccat  | 780  |
| gtcacaattg | agaaggatgg  | tggttgtaat  | cacatggtct  | gtcgtaacca  | gaattgtaaa  | 840  |
| gcagagtttt | gctgggtgtg  | tcttggccca  | tgggaaccac  | atggatctgc  | ctggtacaac  | 900  |
| tgtaaccgct | ataatgagga  | tgatgcaaag  | gcagcaagag  | atgcacagga  | gcgatctagg  | 960  |
| gcagccctgc | agaggtagct  | gttctactgt  | aatcgctata  | tgaaccacat  | gcagagcctg  | 1020 |
| cgctttgagc | acaaactata  | tgctcagggt  | aaacagaaaa  | tggaggagat  | gcagcagcac  | 1080 |
| aacatgtcct | ggattgagggt | gcagttcctg  | aagaaggcag  | ttgatgtcct  | ctgccagtgt  | 1140 |
| cgtgccacac | tcatgtacac  | ttatgtcttc  | gctttctacc  | tcaaaaagaa  | taaccagtcc  | 1200 |
| attatccttg | agaataacca  | agcagatcta  | gagaatgcc   | cagagggtgt  | ctcgggctac  | 1260 |
| cttgaacgag | atatttccca  | agattctctg  | caggatataa  | agcagaaagt  | acaagacaag  | 1320 |
| tacagatact | gtgagagtcg  | acgaagggtt  | ttgttacagc  | atgtgcatga  | aggctatgaa  | 1380 |
| aaagatctgt | gggagtacat  | tgaggactga  | gaatggccct  | gcataaaatg  | aactctgaaa  | 1440 |
| actttaccat | ctagagtgtc  | catgcaatta  | aaacaaaaca  | aacacaaaca  | aggaggcact  | 1500 |
| aagcctatct | tgacaccact  | ggtctgtagt  | accagaattg  | ttttgttaat  | ggaaagttaa  | 1560 |
| agtaaattat | attgtaataa  | aaaggtagat  | aaaccattgt  | acaacagtat  | tctaggccgc  | 1620 |
| caacaaaagt | gtgacagaca  | cactaaaagc  | cctccaactt  | taacttgtaa  | cgtagcttca  | 1680 |
| ttctcaaagc | tgactccttt  | tttttctttt  | tcttttctct  | gagtgtagta  | cagttaaaat  | 1740 |
| ttcaaacagc | tccttgacac  | tgcttttcat  | gttcaaacca  | gccattttgt  | tgtactttgg  | 1800 |
| taaaggacct | cttccccttc  | ctcccctaca  | catacagata  | cacccacaca  | cagactgact  | 1860 |
| ctctttctct | cataccccaa  | ggtcatgagt  | gaatgatgct  | tagttccttg  | taaagaaaat  | 1920 |
| cttgggatgg | ggaaaggggt  | aggcagcaag  | aggattcaac  | aaacgaaaaa  | cataaaaact  | 1980 |
| ttgtatatga | cttttaaaac  | aagaggacaa  | cacagtattt  | ttcaaaattg  | tatatagcgc  | 2040 |
| atatgcatgg | acaaagcaag  | cgtggcacgt  | gtttgcataa  | tgtttaatta  | caaaaaata   | 2100 |
| ttattctttt | aaaaatcttc  | aagattatgt  | ctatttgcgt  | tgcattttct  | ttcagtttgc  | 2160 |
| ttatcttttc | cgggttgggg  | ttgggataaa  | ggtgtgtcgg  | tttagcacct  | ctggaagacc  | 2220 |
| tatctagagc | tcttttactt  | tcctgaggtt  | attttgccc   | ttctgggtgt  | ggtatgtctg  | 2280 |
| ttgccggcca | tgggctncay  | gccttgaatt  | cctgctcttg  | atcagggaca  | agggaggtca  | 2340 |
| agctctgact | aatgccatga  | cctgattaag  | gggtacagca  | gggagttttg  | ttgctacagc  | 2400 |
| tcataaatta | acctgtccca  | acctaatccc  | cctccatggc  | atcatgcctc  | tacccaagcc  | 2460 |
| tttgtgtgcc | catgttatgc  | acacagctgt  | aggcattctt  | aagtcccctg  | tcgcatccag  | 2520 |
| tggaagcatt | ttaaaatttc  | ttttactttt  | tggttttccc  | ttaattgctg  | cttttcagat  | 2580 |
| tttagttatg | gctcgtctgc  | tcaccccttc  | tctacattag  | ggtgtcaaag  | agaatgtttt  | 2640 |
| gctttaaata | taaatagcca  | ttcatttagt  | ctcagattgt  | gaatttaaaa  | tgggtggatac | 2700 |
| cgaaattgct | tgtgtgtgtt  | gctgtgggtt  | tggtttgaag  | gcaaacaccc  | ctagaacatg  | 2760 |
| atattcccat | ctagtgcatt  | taaatagaaa  | tactgagtt   | tgctgctttt  | ttattgtcag  | 2820 |
| cagataggag | aattaataat  | gcatttttagc | tgatgtgtcc  | atttttatga  | aattcctact  | 2880 |
| aagagctatg | ttaaaagtaa  | aggatgggtg  | tggttgtatt  | aactatatac  | ctgttttaggc | 2940 |
| cattctggct | gtgggtatttt | tcaataggtc  | agcatctgta  | aactctgtcag | ttttatacag  | 3000 |
| gagtgcagag | tgaactaggc  | aactagatta  | agaggctctaa | atatgaaata  | ccagttgagg  | 3060 |
| ctgaggacct | cttcgtcttc  | ctttaaatgt  | cttttgccca  | gggagtgttt  | accatttgtg  | 3120 |
| aggcagcttt | gtctgctctt  | acactgtaca  | tcctattact  | ccattgggaa  | gtaggttcac  | 3180 |
| tttctctggt | ccttttgcct  | aagttaggct  | ttgctgaatc  | aaccctactt  | ttccttttag  | 3240 |
| aaaaggttgt | tacaggagat  | ttactggcaa  | ctgttctttt  | cccatcaaaa  | atcagtgaat  | 3300 |
| gtttgctgag | tataaatgct  | gcttccctaa  | accacttgtc  | gctttaggat  | caactttacc  | 3360 |
| tgtacctttt | ctcctttcct  | cccttgccac  | ctcaggtgca  | aactctgaact | cagtgtctgc  | 3420 |
| ttcttccatt | ttctcgtctc  | tctccctctc  | tcccccatta  | tccatatgac  | attattttac  | 3480 |
| ttcaaatgac | agcatcaatc  | ttaaaaagat  | atacattaaa  | actaaggagt  | ttttttaaag  | 3540 |
| aaagctgaa  | taagttcctt  | tccctggtaa  | ctttgaaaag  | cagtcagagt  | tgctatatag  | 3600 |
| atatatgtgg | ctcctttaa   | atgctttgtg  | tatgtgtggt  | gttttaaaaa  | aaaaaaaaaa  | 3660 |
| ttcggggggg | ggcccggtnc  | ccat        |             |             |             | 3684 |

&lt;210&gt; 116

&lt;211&gt; 1965

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (476)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1136)

<223> n equals a,t,g, or c

<400> 116

|   |      |
|---|------|
| aagaaaggggt attaaaattc tagatcacat atggaccggg gaagggttttt naccctctgt | 60   |
| tagtgacatc gagtctccca ctagacaaaa taggtggaaa aatctctcga gggctcacat   | 120  |
| tgttttgtca tcttcaggaa aaacaccacc aggccatacc acagcctgcc cagtggaggc   | 180  |
| gtctttgcca acagcaccgg gatgctgggt gtggcctttg ggctgctggg gctctacatc   | 240  |
| cttctggctt catcttggaa gcgcccagag cgggggatcc tgaccgacag acagcccctg   | 300  |
| ctgcatgatg gggagtgaag cagcaggaag gggctcccaa gagctcctgg tgggtgcagcc  | 360  |
| tgtgtccccc tcagaagctc tgctcttccc agggctcccc gctggtttca gcaggcgact   | 420  |
| ttcttccaat gctgggcca gacttcttgc ctgggtgctg gctgcccctc tccggncgcg    | 480  |
| ttgctgcctg tctgctttcc ttgggtggytt tgctgggtgc tgggcctgcc ctctccggcc  | 540  |
| gcttgctgcc tgtctgcttt ccttggtggc tttgctgggt gctgggcctg ccttctctgg   | 600  |
| ctgcttgctg cctgtctgct ttcccttggtg gctttggctt ctgcactcct tggcgtcasc  | 660  |
| tctcaggtcc tccattcaca cgaggtcctc ctgcctctgg ccgctcttgc tgctcctgtc   | 720  |
| tgaagawac agactgattt cctcttaaga ctccctagga tgtggtgaag agctgggact    | 780  |
| caagtgcagt ccacggtgtg aaacatgagg gargtgaggt gtccgtccac ttccccata    | 840  |
| aaggtgtgca tttcagttag gctgccccgc cacagacag gcttcatctg ctctgccatc    | 900  |
| cagccccatc tggatgtgag gtgggtgga gacatcatgg ggtgattgca gaaaggggga    | 960  |
| gtggcggccc acgcagcttc tgctgaggag ctgaccgctc tgagctgttc tgtttcgtat   | 1020 |
| tgctgctctg tgtctgcatg tattgtgacc gtgcggctcc acctcttcca gctgctgcta   | 1080 |
| cagctgaggg ctggatcccc gcctttccct gtgacttacg tgtctgtcac cggcangcag   | 1140 |
| ccctacaaat cctggtgacc tgctctccca agaacagagc ctgtccccag atgtcccagt   | 1200 |
| agcgtgagt aacagagggt gctgtggact tctctactt ctcttctgtg gatcagggcc     | 1260 |
| ttcttgctc ccgctgggca ggtctggcct tgctctcttg gcagggcccc agcccctctg    | 1320 |
| accactctgc agctcaccat gcagctgatg ccaaagtgtg ggtgtccagt gtgcagcagc   | 1380 |
| cctgggagcc actgccacct tcagaggggt tcttctgtga gaccacatt gcttcacctg    | 1440 |
| gccccacat ggctgcttgc ctggcccaac ctagcgttct gtgccatgct agagcttgag    | 1500 |
| ctgttgctct tcttcagggg aggaaatagg gtggagagcg ggaagggctt tgctcctaag   | 1560 |
| tggtgctgct gtggcttttt tgccttctcc aaagacgcac tgccaggctc caagcttcag   | 1620 |
| actgctgtgc ttagtaagca agtgagaagc ctgggggttt gagcccacct actctctggc   | 1680 |
| agcatcagca tcctactcct ggcaacatca ggccaacgct caccacagcc tcacattgcc   | 1740 |
| agatgttggc agaagggcta atattgaccg tcttgactgg ctggagcctt caaagccact   | 1800 |
| gggatgtcct ccaggcacct ggggtccatg accagctccc cgtctccata ggggtaggca   | 1860 |
| tttcaactgg ttatgaagct cgagtttcat taaatatgtt aagaatcaaa gctgtctttg   | 1920 |
| ttcaggctgc tataacaaaa atataatagc ctgggtggct taaac                   | 1965 |

<210> 117

<211> 503

<212> DNA

<213> Homo sapiens

<400> 117  
 agtgatcccc ttgcctcggc ctcccaaaat gctggaattg taagcgtggg cctctgcacc 60  
 cggcctggtc cgcaatttaa aaacgcacag ccaccattcc ctytccagaa agcaccacaga 120  
 tgcccttggg agaaccagcc tcctccatgg aggaaagctt gggatctgcc tccccacctg 180  
 gggaggagag ggatctgtgg aaaatccttc tgacggactt cccctcagtg cctgatccat 240  
 actcaatagt agaaaaagta agaaatatac aaagatagca gatacacgga gacagttccc 300  
 caaatagctg agcgawtagc gcagaagcaa tattgaagac ctaatagctg agacatttcc 360  
 agaactgata aagtgcattc agccacagat caagcagccc agaaaattcc aggcagcatc 420  
 aacaaataaa tagccccaca tgcacccgtg aaaatgcaga agaccaaaca aaaaagtccg 480  
 gtcaacagcc agagttaaag agg 503

<210> 118  
 <211> 1071  
 <212> DNA  
 <213> Homo sapiens

<400> 118  
 tcgacccacg cgtccggtca ctcccaagat ggccggaccta ctgggctcca tcctgagctc 60  
 catggagaag ccacccagcc tcggtgacca ggagactcgg cgcaaggccc gagaacaggc 120  
 cgcccgctg aagaaactac aagagcaaga gaaacaacag aaagtggagt ttcgtaaaag 180  
 gatggagaag gaggtgtcag atttcattca agacagtggg cagatcaaga aaaagtttca 240  
 gccaatgaac aagatcgaga ggagcatact acatgatgtg gtggaagtgg ctggcctgac 300  
 atccttctcc tttggggaag atgatgactg tcgctatgtc atgatcttca aaaaggagtt 360  
 tgcacctca gatgaagagc tagactctta ccgtcgtgga gaggaatggg acccccagaa 420  
 ggtgaggag aagcggaaagc tgaaggagct ggcccagagg caagaggagg aggcagccca 480  
 gcaggggcct gtggtggtga gccctgccag cgactacaag gacaagtaca gccacctcat 540  
 cggcaaggga gcagccaaag acgcagccca catgctacag gccaataaga cctacggctg 600  
 tgtgcccggt gcccaataaga gggacacacg ctccattgaa gaggctatga atgagatcag 660  
 agccaagaag cgtctgcggc agagtgggga agagtgtccg ccaacctcct aggcgccccg 720  
 cccagctccc tttgacctct ggggcagggc agggggcagg gagagacaag gctgctgcta 780  
 ttagagccca tcctggagcc ccacctctga accacctcct accagctgtc cctcaggctg 840  
 ggggaaaaca ggtgtttgat ttgtcacctg tggagcttgg atatgtgctg ggcattgtgtg 900  
 tgtgtgtgtg atagtgtgaa tgcacagggt ggtatttaac ctgtattatt ccccgttctt 960  
 ggaattttct tycccatggg gctgggggtac ttacattca ataaatactg ttttaaccctaa 1020  
 aaaaaaaaaa aaaaaaraaa raaaaaaaaa aaaaaaaaaa aaaaaaaaag g 1071

<210> 119  
 <211> 1101  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (147)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (376)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (395)  
 <223> n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1101)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 119

|            |            |             |            |            |            |      |
|------------|------------|-------------|------------|------------|------------|------|
| gggcacagct | gaagctgcag | acctccccag  | gggatggctc | ctctcccca  | ggagccccga | 60   |
| ggcaggggag | gcagaaagcc | tgggctcttg  | ggggtggcct | gcggacagct | gtgctgtggg | 120  |
| ccgggggctg | ggcctgtccc | acagggncgt  | ggagctcgtg | gttctgagca | gccagctggg | 180  |
| tggtgtcttg | ggatagctgg | gaggcacagc  | ggctgccatg | tgggactggg | actggagtgc | 240  |
| tccctggctc | tggcctctgt | ggctcagcct  | tgctctggtc | tgcttgagtg | caggggcca  | 300  |
| ggggcacagg | gccagtggg  | ccggccacgc  | tcgggccctc | acctgtgaga | tggggtcgga | 360  |
| atttkacaca | gcctanggct | tggttcttgg  | tkgtngamcg | tggactyctk | agaacgggag | 420  |
| tgctggctct | gaaaggcgtg | gttggagacc  | agctgctttt | ctcgtgtttt | ttctcttagg | 480  |
| agattaaaca | aaaacagaaa | gcacaagacg  | aactcagtag | cagaccccag | actctcccct | 540  |
| tgccagacgt | ggttccagac | ggggagacgc  | acctcgtcca | gaacgggatt | cagctgctca | 600  |
| acgggcatgc | gccggggggc | gtcccaaacc  | tcgcagggtc | ccagcaggcc | aaccggcacc | 660  |
| acggactcct | gggtggcgcc | ctggcgaaact | tgtttgtgat | agttgggttt | gcagcctttg | 720  |
| cttacacggg | caagtacgtg | ctgaggagca  | tcgcgcagga | gtgaggccca | ggcgccgaga | 780  |
| cccaaggcgc | cactgagggc | accgcgcacc  | agagcgtgac | ctcggcaggc | tggacacact | 840  |
| gccacgcaca | ggcagacca  | ccaggctcct  | aggtttagct | tttaaaaacc | tgaaagggga | 900  |
| agcaaaaacc | aaaatgtgtg | actgggcttt  | ggaggagact | ggagcctcag | ccctgtcctg | 960  |
| gccacggggc | gctggggctg | gtgtgggtgg  | gccttgtgtg | ctggatttgt | agcttatctt | 1020 |
| ccgtgttgtc | tttgacctg  | ttttagtaaa  | cccggttttc | attttaaaaa | aaaaaaaaaa | 1080 |
| aaactttggg | ggggggcccc | n           |            |            |            | 1101 |

&lt;210&gt; 120

&lt;211&gt; 282

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 120

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| agcttctctg | tccagtcttg | aactctgggs | tctcttgga  | ctttcctcac | ccctctcagc | 60  |
| ctgaatatcc | cttccatgga | ttccactcaa | ccagactttg | gatctgtgcc | tacttaatca | 120 |
| accttatctt | tgcaatatgt | tcgggcccac | cttccactcc | ttggttcttg | ttcctccttg | 180 |
| gcctaacttg | tcccttctcc | acttcacatc | cccgggtggg | cagcattcct | ccttccctcc | 240 |
| aacctccctc | cgtctcaraa | aaaaaaaaaa | aaaaaaaaaa | tt         |            | 282 |

&lt;210&gt; 121

&lt;211&gt; 2635

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2605)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 121

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| taaggggggtg | tgtgctcacc | tcctcctgac | ccttaacact | cctgtcctgc | ccagaccaac | 60  |
| agagagagct  | gtccctgaga | cccgggagag | aagcagctgc | cgaaagctgc | agcctttccg | 120 |
| cactctgaga  | ccatgatctt | cctcctgcc  | ggggagagcc | acccacaggc | catgtccagc | 180 |
| cccacttccc  | tcagccccc  | gggyttcctt | ctggccctc  | tgaggattcc | ctagggtcgc | 240 |
| ccgcagagg   | ggyttcccca | agctctgttt | tgaagcctgc | aatgtggaaa | agtgagaagt | 300 |
| cagaggggaac | aggacaggtg | cagccgggct | ctgaggccac | acctcacacc | tcgctgttcc | 360 |
| ccaacatccc  | ctgagcagtg | tgagctcatc | tcaccagatg | agaagaggcc | ctgtgcattt | 420 |



|             |             |            |            |             |            |      |
|-------------|-------------|------------|------------|-------------|------------|------|
| yttttgtttg  | tttgttgetg  | ttttccccc  | cccatccagt | tctcctcagc  | aaagcaaatt | 480  |
| ccttaacacc  | tttgggtggag | aatttcttac | ccagacttgg | ggctgtgatg  | cccttcagtg | 540  |
| cgtgggtgagt | gcagcgtgtg  | tgcgtgtgcc | tgtgtgtgaa | cctggggggcc | atcctggtgg | 600  |
| cctgggagcg  | tgaggagagg  | ccccctgtgt | gctgggtgag | tgggtgggtgt | ggggtcaatg | 660  |
| cagtgaggct  | ctctgggtga  | ggctcccaac | ctggcagtc  | ccagcctccc  | agcatctgtg | 720  |
| agcgtctgtt  | ggactttaca  | gaagagcctc | atccygtctg | ccccctactc  | tgccctggaa | 780  |
| tcaacatctt  | ccgagtcctt  | cttgggggaa | atagcagagc | cccacttaac  | tccataaact | 840  |
| gcttcccatt  | ccgcagccca  | gttctgattg | ttgaggtgtc | gcgtcgttcc  | aggtccccc  | 900  |
| gtccccctct  | tctcctgtcc  | tctctctgtc | cttcacctcc | ccactccagc  | cccggctcag | 960  |
| ttcagggaaa  | tgtgtttcca  | yatcagccct | ctgctctctg | aggcagccgc  | gcctctgact | 1020 |
| cggagctact  | tgaacttct   | gctcttgcta | ggattggagt | ctacctatct  | cttcatttgg | 1080 |
| tcccagctgg  | agttctggaa  | ctttcctcct | cgggggtggg | gtgggggttg  | ttaaggatgc | 1140 |
| tggggggcct  | ggggaaggaa  | ggagttcaga | ggaagggtgt | ccccgtcct   | cttgatgtca | 1200 |
| ccctccgctc  | ctgggacacg  | tgtctctct  | gtctctgggt | cttctggctg  | tgacgtttg  | 1260 |
| tgtgtccttg  | taaatatgtt  | ttaggaagaa | agcaaaagg  | actgaactag  | cctctggtag | 1320 |
| gattgcaggg  | gtccagcctt  | gcctgtttcc | gaagccccc  | cactgccttt  | cgccccactg | 1380 |
| agactggtcc  | cctcaaaagg  | tagacaaaac | agcagctccc | tgtggagctg  | aagggcggcc | 1440 |
| tcaaagtggc  | tttttgttag  | acaaggttaa | ggtttctca  | tgagcaaggt  | tgcatatcgg | 1500 |
| tccttctctc  | gctccttgat  | ttgtgacctt | gaccaagggg | cctgccaccc  | agccctcca  | 1560 |
| gtgccctctc  | ctcgatgcct  | cgctccttcc | tgccccact  | ccccgtgctt  | aggcaggtag | 1620 |
| gggaattagg  | gccatgctgg  | aagaagctta | accatgtgtt | caaagaacgg  | tttcttgctt | 1680 |
| gcttggctct  | ggaactcccc  | ttggctgccc | caggcctcct | tggcccatgg  | gtgctggggg | 1740 |
| aggtggatgt  | cagatctggt  | aggttgacgc | agagaaaata | aatgtgcctt  | gagagaccac | 1800 |
| tcagagaggg  | tccaagggtg  | atggagaagg | aagcatggcc | tgggagcttg  | gaaggarggg | 1860 |
| gtggtgggtg  | gcggcatctt  | gactgcccc  | tgttgtccca | cacgtggggg  | gtggtcacc  | 1920 |
| cycttcactc  | cagcccgctt  | gccttcagcc | ttccatgagc | ttcacctgct  | tccaacttca | 1980 |
| ctttggaggg  | ggtgggtgct  | gttggcatca | acacggggac | cctctgcttc  | accaaaagcc | 2040 |
| gagccctcag  | cccctgggga  | gaacaaatgg | ctgagctttg | atacctgggg  | tcgtcgagag | 2100 |
| gctgcgggct  | ggcggcagtc  | ccaggggaga | gacaccacag | aaggagaccc  | agacatccc  | 2160 |
| aggaagttcc  | cagcagagca  | aactgctttc | cagcctgaag | cctgcttaaa  | ctgtgtgatg | 2220 |
| tgcaataact  | gagcttagag  | ttaggaattg | tgttcaagtg | cttggatttc  | cgtctgtaga | 2280 |
| tttaactgct  | gaaattgtat  | ctctcagtaa | ttttagatgt | cttttaaaaa  | attgaaaaac | 2340 |
| aaagtgttag  | actgtgtgcg  | tgtgcgttga | tgggcactca | agagtcccgt  | gagtcacca  | 2400 |
| gcctgcctt   | tccccgtcgc  | ccccatcctc | tcacgtccc  | cccygcctcc  | acttggggac | 2460 |
| cctgcctcgt  | gtcgtcttta  | tctgcctatt | actcagccta | aggaaacaag  | tacactccac | 2520 |
| acatgcataa  | aggaaatcaa  | atgttatatt | taagaaatg  | gaaaataaaa  | actttataaa | 2580 |
| caccaaaaaa  | aaaaaaaaaa  | accnnggggg | ggggccggta | accatttctg  | cctaa      | 2635 |

&lt;210&gt; 122

&lt;211&gt; 994

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 122

|            |            |            |             |            |            |     |
|------------|------------|------------|-------------|------------|------------|-----|
| gaattcggca | gaggttcggc | gaagataggg | aataaggaag  | cacaggagta | ggggagaagg | 60  |
| aagcacagga | gtaggggaga | tatacagcgg | tcaggataag  | ggggaaaggg | cggtggttgc | 120 |
| scaagaggtg | aaacaagatg | tgagagacaa | ggggtagggg  | agaaatgggg | cagcggttag | 180 |
| gttcagaagc | gcatagaccg | tggcggacgg | gcaatgcgag  | gggcacagaa | aggaactgag | 240 |
| gggtgggcta | ttttaargga | gatggctcct | cagccctctt  | ytcttctgcg | tagttctcct | 300 |
| ctccagggc  | gcgcgcggat | atgtogtccg | gaaaccagcc  | cagtctaggc | tggatgatga | 360 |
| cccacctcct | tctacgctgc | tcaaagacta | ccagaatgtc  | cctggaattg | agaaggttga | 420 |
| tgatgtcgtg | aaaagactct | tgtcttttga | aatggccaac  | aagaaggaga | tgctaaaaat | 480 |
| caagcaagaa | cagtttatga | agaagattgt | tgcaaaccca  | gaggacacca | gatccctgga | 540 |
| ggctcgaatt | attgccttgt | ctgtcaagat | ccgcagttat  | gaagaacact | tggagaaaca | 600 |
| tcgaaaggac | aaagcccaca | aacgctatct | gctaattgagc | attgaccaga | ggaaaaagat | 660 |
| gctcaaaaac | ctccgtaaca | ccaactatga | tgtcttttga  | aagatatgct | gggggctggg | 720 |
| aattgagtac | accttcccc  | ctctgtatta | ccgaagagcc  | caccgccgat | tcgtgaccaa | 780 |

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gaaggctctg | tgcattcggg | ttttccagga | gactcaaaag | ctgaagaagc | gaagaagagc | 840 |
| cttaaaggct | gcagcagcag | cccaaaaaca | agcaaagcgg | aggaacccag | acagccctgc | 900 |
| caaagccata | ccaaagacac | tcaaagacag | ccaataaatt | ctgttcaatc | atttaaaaaa | 960 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaagggga | gggg       |            |            | 994 |

&lt;210&gt; 123

&lt;211&gt; 2537

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 123

|            |            |             |             |             |             |      |
|------------|------------|-------------|-------------|-------------|-------------|------|
| ggcacgagcc | acctcggccc | cgggctccga  | agcggctcgg  | gggcgccttt  | tcggtcaaca  | 60   |
| tcgtagtcca | ccccctcccc | atccccagcc  | cccggggatt  | caggctcgcc  | agcggccagc  | 120  |
| cagggagccg | gcggggaagc | gcgatggggg  | ccccagccgc  | ctcgctcctg  | ctcctgctcc  | 180  |
| tgctgttcgc | ctgctgctgg | gcgcccggcg  | gggccaacct  | ctcccaggac  | ggctactggc  | 240  |
| aggagcagga | tttgagctg  | ggaactctgg  | ctccactcga  | cgaggccatc  | agctccacag  | 300  |
| tctggagcag | ccctgacatg | ctggccagtc  | aagacagcca  | gccctggaca  | tctgatgaaa  | 360  |
| cagtgtgtgc | tggtggcacc | gtggtgctca  | agtgcgaagt  | gaaagatcac  | gaggactcat  | 420  |
| ccctgcaatg | gtctaaccct | gctcagcaga  | ctctctactt  | tggggagaag  | agagcccttc  | 480  |
| gagataatcg | aattcagctg | gttacctcta  | cgccccacga  | gctcagcatc  | agcatcagca  | 540  |
| atgtggccct | ggcagacgag | ggcgagtaca  | cctgctcaat  | cttcactatg  | cctgtgcgaa  | 600  |
| ctgccaagtc | cctcgtcact | gtgctaggaa  | ttccacagaa  | gcccacatc   | actggttata  | 660  |
| aatcttcatt | acgggaaaaa | gacacagcca  | ccctaaactg  | tcagtcttct  | gggagcaagc  | 720  |
| ctgcagcccg | gctcacctgg | agaaaggggtg | accaagaact  | ccacggagaa  | ccaaccgca   | 780  |
| tacaggaaga | tcccaatggt | aaaaccttca  | ctgtcagcag  | ctcggtgaca  | ttccagggtta | 840  |
| cccgggagga | tgatggggcg | agcatcgtgt  | gctctgtgaa  | ccatgaatct  | ctaaagggag  | 900  |
| ctgacagatc | cacctctcaa | cgcatggaag  | ttttatacac  | accaactgcg  | atgattaggc  | 960  |
| cagaccctcc | ccatcctcgt | gagggccaga  | agctgttgct  | acactgtgag  | ggtcgcggca  | 1020 |
| atccagtccc | ccagcagtac | ctatgggaga  | aggagggcag  | tgtgccaccc  | ctgaagatga  | 1080 |
| cccaggagag | tgccctgatc | ttccctttcc  | tcaacaagag  | tgacagtggc  | acctacggct  | 1140 |
| gcacagccac | cagcaacatg | ggcagctaca  | aggcctacta  | caccctcaat  | gttaatgacc  | 1200 |
| ccagtccggt | gccctcctcc | tccagcacct  | accacgccat  | catcggtggg  | atcgtggctt  | 1260 |
| tcattgtctt | cctgctgctc | atcatgctca  | tcttctcctg  | ccactacttg  | atccggcaca  | 1320 |
| aaggaacctt | cctgacacat | gaggcaaaaag | gctccgacga  | tgctccagac  | gcggacacgg  | 1380 |
| ccatcatcaa | tgagaagggc | gggcagtcag  | gaggggacga  | caagaaggaa  | tatttcatct  | 1440 |
| agaggcgctt | gcccacttcc | tgcgcccccc  | aggggcccctg | tggggactgc  | tggggcccgtc | 1500 |
| accaaccggg | acttgtacag | agcaaccgca  | gggcccggccc | tcccgttgc   | tccccagccc  | 1560 |
| acccaccccc | ctgtacagaa | tgtctgcttt  | gggtgcggtt  | ttgtactcgg  | tttggaatgg  | 1620 |
| ggagggagga | gggcgggggg | aggggagggg  | tgccctcagc  | cctttccgtg  | gcttctctgc  | 1680 |
| atgtgggtta | ttattatttt | tgtaacaatc  | ccaaagcaaa  | tctgtctcca  | ggctggagag  | 1740 |
| gcaggagccc | tggggtgaga | aaagcaaaaa  | acaaacaaaa  | aacaaaacc   | tggagtgtta  | 1800 |
| ggaggagagt | gaaggtagag | gggtgaggaa  | gggtaagggg  | cagggctggt  | ttcagctggg  | 1860 |
| ggctctcacc | agccctcctt | tcagcctcta  | caacagagca  | gcttcccaga  | cttctccagg  | 1920 |
| aaccagaaa  | cgggatggtt | gtcggcaaaag | ggtgggagtg  | gcttttccctc | tggtagccac  | 1980 |
| acacctgagc | actacggaca | gggaggcagg  | tgccaccttg  | acacctctct  | tccatagcaa  | 2040 |
| tgggaaagtg | atgagtgcgg | gagtcctgag  | gagatgtggc  | ctgcagacaa  | catgcagcca  | 2100 |
| tgcagggacc | caggactgta | acctggggag  | gacgcgggtc  | cctgcaagga  | agagtagatt  | 2160 |
| tggagaggaa | ggatggaggt | ggactctcac  | ccatttcccc  | ccggaatga   | acaaagccgg  | 2220 |
| gccctttcca | taggaactgc | cottggagat  | agcagagtgt  | ggctgcccct  | cettgctcca  | 2280 |
| gcagcagtg  | gagaggcact | gctctggggc  | ctgaactgcc  | tctgcttccc  | ccctgaggg   | 2340 |
| gcccctcact | cttacccaag | actctggatt  | gttgacggc   | aaccactcct  | cccatggcat  | 2400 |
| tgctcagcaa | ctacttctcc | cttcccggcc  | accctgtgcc  | cccttccctg  | tcccaacgcc  | 2460 |
| agcccttcat | ccttctctcc | tcagcagcca  | ggcagacata  | acaacaaaac  | tactaaaagg  | 2520 |
| aaaaaaaaaa | aaaaaaa    |             |             |             |             | 2537 |

<210> 124  
 <211> 1390  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (498)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (499)  
 <223> n equals a,t,g, or c

<400> 124  
 caagctctaa tacgactcac tataggga aa gctgggtacgc ctgcagggtac cgggtccggaa 60  
 ttcccggggtc gaccacgcgc tccgggcctc aggggtggacg catgggttctg cactgaggcc 120  
 ctcgctcatgg tggcgccctgt gtgggtacttg gttagcggcgg ctctgctagt cggctttatc 180  
 ctcttcctga ctgcagccg gggccggggcg gcatcagccg gccaaagagcc actgcacaat 240  
 gaggagctgg caggagcagg cggggtggcc cagcctgggc ccctggagcc tgaggagccg 300  
 agagctggag gcaggcctcg gcgccggagg gacctgggca gccgcctaca ggcccagcgt 360  
 cgagcccagc ggggtggcctg ggcagaagca gatgagaacg aggaggaagc tgtcatccta 420  
 gccaggagg aggaaggtgt cgagaagcca gcggaaaytc acctgtcggg gaaaattgga 480  
 gctaagaaac tgcggaannt ggaggagaaa caagcgcgaa aggccagck tgaggcagag 540  
 gaggctgaac gtgargwgcg gaaacgactc gagtcccagc gcgaatgagt ggaagaagga 600  
 ggaggagcgg cttcgccctgg aggaggagca gaaggaggag gaggagagga aggcccgca 660  
 ggagcaggcc cagcgggagc atgaggagta cctgaaactg aaggaggcct ttgtggtgga 720  
 ggaggaaggc gtaggagaga ccatgactga ggaacagtcc cagagcttcc tgacagagtt 780  
 catcaactac atcaagcagt ccaaggttgt gctcttgga gacctggctt cccaggtggg 840  
 cctacgcact caggacacca taaatcgcat ccaggacctg ctggctgagg ggactataac 900  
 aggtgtgatt gacgaccggg gcaagttcat ctacataacc ccagaggaac tggccgccgt 960  
 ggccaacttc atccgacagc ggggcccgggt gtccatcgcc gagcttgccc aagccagcaa 1020  
 ctccctcatc gcctggggcc gggagtcctc tgcccaagcc ccagcctgac cccagtcctt 1080  
 cctcttgga ctcagagttg gtgtggccta cctggctata catcttcata cctccccacc 1140  
 atcctgggga agtgatggtg tggccaggca gttatagatt aaaggcctgt gagtactgct 1200  
 gagcttggtg tggcttggtg tggcagaagg cctggcctag gatcctagat aagcaggtga 1260  
 aatttaggct tcagaatata tccgagaggt ggggagggtc ccttggaagc tgggtgaagtc 1320  
 ctgttcttat tatgaatcca ttcattcaag aaaatagcct gttgcaaaaa aaaaaaaaaa 1380  
 aaaaactcga 1390

<210> 125  
 <211> 1288  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1286)  
 <223> n equals a,t,g, or c

<400> 125  
 ggcgcgcggg tgaaaggcgc attgatgcag cctgcggcgg cctcggagcg cggcggasca 60  
 gacgtgaac acgttcctct cctcgggtctc ctccgcctcc agctccgcgc tgcccggcag 120  
 ccgggagcca tgcgaccca gggccccgcc gcctccccgc agcggctccg cggcctcctg 180  
 ctgctcctgc tgctgcagct gccgcgcgc tgagcgcct ctgagatccc caaggggaag 240

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| caaaaggcgc | atccggcaga | gggaggtggt | ggacctgtat | aatggaatgt | gcttacaagg | 300  |
| gccagcagga | gtgcctggtc | gagacgggag | ccctggggcc | aatggcattc | cgggtacacc | 360  |
| tgggatccca | ggtcgggatg | gattcaaagg | agaaaagggg | gaatgtctga | gggaaagctt | 420  |
| tgaggagtcc | tggacaccca | actacaagca | gtgttcatgg | agttcattga | attatggcat | 480  |
| agatcttggg | aaaattgcgg | agtgtacatt | tacaaagatg | cgttcaaata | gtgctctaag | 540  |
| agttttgttc | agtggctcac | ttcggctaaa | atgcagaaat | gcatgctgtc | agcgttggtg | 600  |
| tttcacattc | aatggagctg | aatgttcagg | acctcttccc | attgaagcta | taattttatt | 660  |
| ggaccaagga | agccctgaaa | tgaattcaac | aattaatatt | catcgcaact | cttctgtgga | 720  |
| aggactttgt | gaaggaattg | gtgctggatt | agtggatggt | gctatctggg | ttggcacttg | 780  |
| ttcagattac | ccaaaaggag | atgcttctac | tggatggaat | tcagtttctc | gcatcattat | 840  |
| tgaagaacta | ccaaaataaa | tgctttaatt | ttcatttgct | acctcttttt | ttattatgcc | 900  |
| ttggaatggt | tcacttaaat | gacattttta | ataagtttat | gtatacatct | gaatgaaaag | 960  |
| caaagctaaa | tatgtttaca | gaccaaagtg | tgatttcaca | tgtttttaaa | tctagcatta | 1020 |
| ttcattttgc | ttcaatcaaa | agtggtttca | atattttttt | tagttgggtt | gaatactttc | 1080 |
| ttcatagtca | cattctctca | acctataatt | tgggaatatt | gttgtggtct | tttgtttttt | 1140 |
| ctcttagtat | agcattttta | aaaaaatata | aaagctacca | atctttgtac | aattttgtaa | 1200 |
| tgtaagaat  | tttttttata | tctgttaaat | aaaaattatt | tccmacaacc | ttaaaaaaaa | 1260 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaanaa   |            |            |            | 1288 |

&lt;210&gt; 126

&lt;211&gt; 1517

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (159)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1123)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1510)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 126

|             |             |            |             |            |             |      |
|-------------|-------------|------------|-------------|------------|-------------|------|
| agtggcttaa  | aggcatcggt  | ttagggatta | ctgggaagta  | tcttcaaagt | aatacatgag  | 60   |
| aaacattcct  | tcctaaatcc  | tttattatat | tgaatatcgt  | attaattggt | tttcagaggt  | 120  |
| taaattaacc  | atgtattcct  | gcaataaatg | tcacttgtnt  | cttgtatata | atctttttta  | 180  |
| tatattaccg  | gattgattca  | ttagtatttt | gttgaggatt  | tttgtgtcta | tattcataag  | 240  |
| agatgctggt  | ctgcagtttt  | ctttttttgt | gataatctgg  | tttttgtatc | agtaatacac  | 300  |
| gccccatgaa  | acgagttggg  | aagtgttcac | ctctcttgta  | ttttttcaag | agtttgtgaa  | 360  |
| gaattgctat  | taattcttta  | aatgtttggt | agaactctacc | attgaaatca | tgtgtcctgg  | 420  |
| gctttttttt  | gagggagtg   | ttctgataac | taattcagta  | tctacttttt | atagctctgt  | 480  |
| tcagattttg  | cttcttcctg  | agttagtttt | ggtaatttgt  | gtatctctag | gartttgtcc  | 540  |
| atttcattta  | tctcatttgt  | tggcataaat | taaactaaat  | ttggcctgag | cctacctgta  | 600  |
| tatcttgagt  | ccctctgtaa  | ggaactgtag | cctaacttgt  | acataaaca  | actgaaatcc  | 660  |
| taaattagga  | atgtagtttt  | tgtaacagct | cctgagtcct  | aggcagtcac | agcagycaag  | 720  |
| tctgtcaatt  | gcaggctgct  | aactaagcag | cccagtgstca | aatgaggcaa | aaacctttgc  | 780  |
| tttttaacaca | tagtatagct  | ttgtaatcct | tttcttgcac  | actcgggtaa | tttcttcctt  | 840  |
| tttcattccc  | kgwatthttcc | akgaatatga | rtctyccttt  | tttccctccc | tgctcagtcta | 900  |
| gctaattggt  | tgtcaatttt  | gttgatcttt | tgaaraacaa  | acctttgggt | ccactttctt  | 960  |
| gttgcataatg | ctgartattc  | tcataattgg | agtggaaagc  | tgatctttga | ttactttatt  | 1020 |

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| tacttagggc | tgaggagttc | atggacttcg | caaaacctcc | ttgaatctaa | attgcatctt | 1080 |
| ctttcctggt | ttctgggctg | aaacatgttt | tttcccatct | wanawaccct | tggtcttttc | 1140 |
| atkggcgatt | aagactagag | aaagttctag | atmccttgtc | cttttatgct | gtcattttgt | 1200 |
| ttaaaggctt | tctatgtagt | aaaactatct | atatagacaa | aatagagcct | tgagttgtgg | 1260 |
| tcttgaattt | gatcaacatg | atttaccaca | ttctgtactg | gatatttctt | cacctgctgc | 1320 |
| tactgtaaac | cattttattc | ttggatcttc | tgtagagtat | attatcacag | gtacttttta | 1380 |
| caggggtgtc | taatcttttg | gcttccctgg | gcacattgaa | agaagaagaa | ttgtcttggg | 1440 |
| ccacacatca | aatacgctaa | cactaataat | agttgatgag | ctaaaaaaaa | aaaaaaaaag | 1500 |
| gcaaaaaagn | cccaaaa    |            |            |            |            | 1517 |

<210> 127  
 <211> 1073  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (495)  
 <223> n equals a,t,g, or c

|            |            |
|------------|------------|
| <400> 127  |            |
| tgaatctatt | ctttgaacat |
| ttctgcagtg | tgaaatagat |
| cacaggcctt | tttgcaaag  |
| aatatatgtc | tccatctggt |
| aacttggtcc | aatagtccaa |
| aggaagtcca | aaaagcagaa |
| ctgcagagct | gtatcttcag |
| ggtatggwtc | tccttaccct |
| aagtcaaacg | taagntgaaa |
| aggatgtaga | ccagtgtctg |
| tcaataagca | gcctactgaa |
| ccacacaatt | gacaaatgat |
| ctttctgtag | gagaattgaa |
| agagttatgt | gtagtctca  |
| attagatatt | ggtgtcagaa |
| ataatgtatc | ttatgtatgt |
| aattatttaa | tctgatatgt |
| catgcattta | aaaataaagc |
|            | ttaaacaact |
|            | gtaaaaaaaa |
|            | aaaaaaaaaa |
|            | ctc        |
|            | 60         |
|            | 120        |
|            | 180        |
|            | 240        |
|            | 300        |
|            | 360        |
|            | 420        |
|            | 480        |
|            | 540        |
|            | 600        |
|            | 660        |
|            | 720        |
|            | 780        |
|            | 840        |
|            | 900        |
|            | 960        |
|            | 1020       |
|            | 1073       |

<210> 128  
 <211> 300  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (273)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (294)  
 <223> n equals a,t,g, or c

<400> 128

80

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| caacccctgc  | cttttttttg | ttttccattt | gcttggtaga | tcttcctcca | tccctttatt | 60  |
| ttgagcctat  | gtgtgtctct | gcccgtgaga | tgagtctcct | gaatacagca | cacttactgg | 120 |
| tcttgactct  | gtatccaatt | tgccagtctg | tgtctttcat | ttggagcatt | tagcccattt | 180 |
| acatttaagg  | tkaatattgt | tatgtgtgaa | tttratcytr | tcattatgwt | gttagctggg | 240 |
| tatttttgctt | gttagttgat | gcagtttctt | ccnggcacat | atggtcttta | caanttggca | 300 |

&lt;210&gt; 129

&lt;211&gt; 1275

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1152)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 129

|             |             |            |             |             |             |      |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| ggcagagcct  | gtccctgctg  | cccctgcaaa | aaaaaccccc  | tctgggtgtga | gcaggatggg  | 60   |
| tgagggttat  | gtgagctcct  | tctcctttcc | tccagtttcc  | tcttcccttc  | tcctccctgc  | 120  |
| ctcttttgct  | tttccctttc  | ttcctggtag | cccctgcccc  | ttcctgtatt  | ttctcccatc  | 180  |
| gccattctcc  | cctctcccac  | tgtccctaac | ccgttcaaac  | tctttcctct  | taaatgggtg  | 240  |
| agattttctc  | tcaccaagca  | caccccagta | ttaattaaac  | tagctgcaaa  | caggcagcaa  | 300  |
| gtgggtctacc | atgacagatg  | ggttttgtgt | gtgtgtgtgt  | gtgtgttaatt | gtaataaaac  | 360  |
| atattgartc  | actcaataaa  | cacagagtgt | ctactacatg  | tatcargcac  | tatcatagat  | 420  |
| gctaattaac  | gaaactgaaa  | tgccagggcc | ctcacagtgg  | ctcatgccta  | taatcccgag  | 480  |
| actttgggag  | gatgaggcag  | gaggatcact | tgaggccggg  | agttcaagac  | cagcctgggg  | 540  |
| aacatagtaa  | gactccatct  | ctacaaaaaa | aaaatttttt  | ttattatact  | ttaagttttg  | 600  |
| ggttacatgt  | gcagaacgtg  | tagttttggt | acatagggtat | atacgtgccc  | tggtagtgtg  | 660  |
| ctgcacccat  | caacccatca  | cctacattag | gtattttctc  | taatgttacc  | cctctcctag  | 720  |
| ccccccaccc  | cgtgacaggg  | cctgggtgtg | gatgttcccc  | tcctgtgtgc  | catgtgttct  | 780  |
| cattgggtcaa | ctctcaccta  | tgagtgagga | acatgtggta  | tttggttttc  | tgatcttggt  | 840  |
| atagcttgct  | gagaatgtkg  | gtttccagct | ttatccacgt  | ccctgcaaag  | ggcataaaact | 900  |
| catccctttt  | tatggctgca  | tagtggtcca | tggtgtatac  | gtgccacatt  | ttcttaatct  | 960  |
| atcattgatg  | gacaagtgtt  | gctattgtga | atagtgccac  | aataaacata  | cgtgtgcgtg  | 1020 |
| tgtctttata  | gcagcatgat  | ttataatcct | ttgggtatat  | acccagtaat  | gggatcactg  | 1080 |
| agtcaaattg  | tattttctcgt | tctagatccg | taagggaattg | ccacactgtc  | ttccacaatg  | 1140 |
| tttgaactaa  | tntacactcc  | caccaacagt | gtaaaagtgt  | ttctattttt  | ccacaacctc  | 1200 |
| tccaacatct  | gttatttcct  | gactttttta | tgaacgtcat  | tctaactggc  | gtgagatggg  | 1260 |
| atctcattgt  | ggttt       |            |             |             |             | 1275 |

&lt;210&gt; 130

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (471)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

<221> SITE  
 <222> (472)  
 <223> n equals a,t,g, or c

<400> 130  
 cngaaacccc gtgaaccctc cccgggttaa aaagccccc ctaaattgggg ggaacgcytc 60  
 acacgttata aaaaagcact agaattgttt gaaagcgaga aacaacagct gtgtagggtta 120  
 gctagcagtt agtgttgtag agaagacaga tatttgtaga tttgtgcatt ttctaagttt 180  
 gctgcaatga gcatgtatta ctttcatagt tataaaacac atgcaaaatg ccctttttaa 240  
 atgaaaaaaa atccatgagt gtaagtata tatatgcttt ggaaagcctg ggacgggcat 300  
 tgtttactct caatagtagt tggttgccct tgtctttttg agacattttg ttttaactctg 360  
 ttgatgacaa taacctgttg ataataaac ttgataacaa ataaaatgac ttatgattga 420  
 awmaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nn 472

<210> 131  
 <211> 1950  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (132)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (225)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (249)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (577)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1933)  
 <223> n equals a,t,g, or c

<400> 131  
 acctctcaga atcttctctc agcaacctga gtcttcgccc ttccctcagag cgccctcagtg 60  
 acacccctgg atccttccag tcaccttccc tggaaattct gctgtccagc tgcctccctgt 120  
 gccgtgcctg tnattcgctg gtgtatgatg aggaaatcat ggctggctgg gcacctgatg 180  
 actctaacct caacacaacc tgccccttct gcgcctgccc cttntgccc ctgctcagtg 240  
 tccagaccnt tgattcccgg cccagtgtcc ccagcccaa atctgctggt gccagtggca 300  
 gcaaagatgc tccgtgccct ggtggtccct gccctgtgct cagtgaccga agctctgcct 360  
 tgcctctggat gagccccagc tctgcaacgg gcacatgggg ggagcctccc ggcggttgga 420  
 gagtggggca tgggcatacc tgagccccct ggtgctgctg aaggagctgg agtcgctggg 480  
 agagaacgag ggcagtggag tgctggcggt gccctgaactg ccctctgccc accccatcat 540  
 cttctggaac cttttgtggg atttccaacg gctacgncct cccagtattc taccaggcct 600  
 ggtgctggcc tccgtgtgat ggccctcgma ctcccaggcc ccatctcctt ggctaaccct 660  
 tgatccagcc tctgttcagg tacggctgct gtgggatgta ctgaccctg accccaatag 720

|             |            |            |            |             |             |      |
|-------------|------------|------------|------------|-------------|-------------|------|
| ctgcccacct  | ctctatgtgc | tctggagggt | ccacagccag | atccccccagc | gggtggatatg | 780  |
| gccaggccct  | gtacctgcat | cccttagttt | ggcactgttg | gagtcagtgc  | tgcgccatgt  | 840  |
| tggactcaat  | gaagtgcaca | aggctgtggg | gctcctgctg | gaaactctag  | ggccccacc   | 900  |
| cactggcctg  | cacctgcaga | ggggaatcta | ccgtgagata | ttattcctga  | caatggctgc  | 960  |
| tctgggcaag  | gaccacgtgg | acatagtggc | cttcgataag | aagtacaagt  | ctgcctttaa  | 1020 |
| caagctggcc  | agcagcatgg | gcaaggagga | gctgaggcac | cggcgggcgc  | agatgccac   | 1080 |
| tcccaaggcc  | attgactgcc | gaaaatgttt | tggagcacct | ccagaatgct  | agagacctta  | 1140 |
| agcttccctc  | tccagcctag | ggtggggaag | tgaggaagaa | gggattctag  | agttaaactg  | 1200 |
| cttccctggt  | gccttcatgg | agttgggaac | aggctgggaa | ggatgccag   | tcaaaggctc  | 1260 |
| caagcgagga  | caacaggaag | agggatccac | tgttaccaa  | agtcctgatt  | ccccatcac   | 1320 |
| caacctaccc  | agtttggtcg | tgctgatgtt | gggggagatc | tggggggagt  | tggtacagct  | 1380 |
| ctgttcttcc  | cttgctctat | accgggaact | cccctccagg | gtaccacag   | atctgcattg  | 1440 |
| ccctgggtcat | tttagaagtt | ttgtttta   | aaaacaactg | gaaagatgca  | gagctactga  | 1500 |
| gcctttgccc  | tgaatgggag | gtagggatgt | cattctccac | caataatggt  | ccctcttccc  | 1560 |
| tgacgttgct  | gaaggagccc | aaggctctcc | atgcctttct | acctaagtgt  | ttgtatttta  | 1620 |
| ttttaaat    | tttattctgg | agccacagcc | cccttgctta | tgaggttctt  | atggagagt   | 1680 |
| agaaagggaa  | gggaaatagg | gcaccatggt | ccggtgggtt | gtagttcctt  | caaagtcagg  | 1740 |
| cactgggagc  | tagaggagtc | tcaagctccc | cttaggaaga | actgggtgcc  | cctccagtc   | 1800 |
| taatttttct  | tgccctgccc | gccttgggga | atgcctcacc | cacccaggct  | ctgacctgtg  | 1860 |
| caataaggat  | tgttccctgc | gaagttttgt | tggatgtaaa | tatagtaaaa  | gctgcttctg  | 1920 |
| tctttttcaa  | aaaaaaaaa  | aaaaaaaaa  |            |             |             | 1950 |

<210> 132  
 <211> 990  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (657)  
 <223> n equals a,t,g, or c  
  
 <220>  
 <221> SITE  
 <222> (852)  
 <223> n equals a,t,g, or c  
  
 <220>  
 <221> SITE  
 <222> (859)  
 <223> n equals a,t,g, or c  
  
 <220>  
 <221> SITE  
 <222> (962)  
 <223> n equals a,t,g, or c

|             |            |
|-------------|------------|
| <400> 132   |            |
| tggaagattt  | aaaatagggt |
| cttgagtcct  | tattattatg |
| agcctgatct  | ttttcatatt |
| gaaatgtatt  | tttgcatgtt |
| cttttaagca  | tgatattttt |
| atattttacat | gtaatgtaat |
| ttattttatc  | tagggcattt |
| aycattgtat  | tttccycat  |
| tttcagaatt  | gcaatatgcc |
| tcattttct   | tttgaatatt |
| aatatataag  | cttgaataag |
| accaaagctt  | cttatattaa |
| ctgtggatta  | acatttccat |
| actttttgtg  | tctttatata |
| aatctycacc  | ttttacttgt |
| tattatttaa  | ccaacctatt |
| tgtattaatc  | aaatattttt |
| yaaatatata  | ttgtggstat |
| aacctaaatt  | attactttta |



|            |            |            |             |            |             |     |
|------------|------------|------------|-------------|------------|-------------|-----|
| ccacttactt | gaaaattctg | gaactttaga | acattttattg | ttttatgcat | tttaattcta  | 600 |
| cttgtatttt | tactactcct | aaacattatt | attgttttag  | acaagccaaa | atataatnttg | 660 |
| ttattatctt | atctccatt  | tctttctgta | tttttatgcc  | actatgtatg | ctcaatttcc  | 720 |
| ttctatgtga | tgaacctaat | tcagtacttt | tgttttttaa  | tctgtgcagg | tagcctggcc  | 780 |
| attaaatfff | tatttttggg | ttgctgaaaa | aattgtgttt  | atttctatat | gcatacttat  | 840 |
| gcataataga | tnctaggtng | acataatfff | agtattttata | aatgtaaagt | cattwatktg  | 900 |
| gcttctatca | tttckgtkga | gaaatcaatt | gtcagcccaa  | tagtttttca | ttttaaatta  | 960 |
| cngaattfff | tcattgtctt | ggttttagga |             |            |             | 990 |

&lt;210&gt; 133

&lt;211&gt; 1720

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 133

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| gtctgataag  | cgactgtggg | tattccccta  | aagtttactt  | cagcactaac  | actagtgcct  | 60   |
| ccgctggagt  | ttgcagtttt | ccagctttat  | acaggatttt  | cctttgactg  | gaagagtcaa  | 120  |
| ggataatagag | actcaacagt | gacattttat  | gtacaacatc  | aaggggaata  | ggatactcat  | 180  |
| caaaactggga | ttattcttat | caaaacatgg  | tcttctttga  | ataagaaaaa  | tacatagttg  | 240  |
| gttattatgg  | acttaaaact | gtgttaaatg  | gatatctctga | taaaatattt  | gctgctctgt  | 300  |
| agagtgtgga  | aaatctgaga | atattagctt  | tactcatctt  | gagctttgag  | gatgttctct  | 360  |
| gtacgcogat  | ggtttcatat | taactaaaaa  | agctgggtat  | tgtaaaatct  | catttataaa  | 420  |
| aactcagatg  | agaagaaaat | tttctttgat  | ggtgagactg  | ttgtcttagt  | tcaggaaaat  | 480  |
| atttaataat  | cctttgttac | ctgtgaatga  | aggaactttg  | taattctgat  | ttatcgtaaa  | 540  |
| acatgagcct  | ttccagagtc | agcttagaca  | ctgtttgcgc  | aaatagccat  | gctttgcctt  | 600  |
| atgccaaagga | ggcccagagg | gagggcctag  | tcttctcttg  | ttgctgtaca  | tatattgaaa  | 660  |
| tgcttttttt  | ttttattttg | catttgttat  | ctataatgag  | ccttctgagc  | cctgatatta  | 720  |
| tgtgagacaa  | acaggagtta | ttgatgttat  | acaactccct  | ccattcagga  | ttttctgctt  | 780  |
| ggagggaat   | atgttgacct | tagagaattg  | tgaatattgt  | tgcaattctt  | gaatatatta  | 840  |
| ccatgtgaat  | aatagagact | gtgttgctct  | ctagtataag  | ctatatttat  | ttttgattca  | 900  |
| tttgaattac  | tagttataac | tggagaaatt  | ttgttacctc  | tatcctggct  | tgccctgactg | 960  |
| gctgtataat  | agcagcagcc | tcttttagag  | catcttaatg  | aaaacatgga  | tgaaaggaat  | 1020 |
| taatgatgat  | atctgcagac | tgcgtagaaa  | atggcttttg  | ttcccagcgt  | taacattttc  | 1080 |
| ttctcaatca  | catttcaatg | tttgtggaga  | gtggcagatt  | cacaccagaa  | acactagggtg | 1140 |
| ttcatatcca  | tagcatggat | gcagaataag  | cagttgggag  | agaagcttct  | tcctacctgg  | 1200 |
| tactcctccc  | attcacctca | gcccagcccc  | agacaggcgt  | tagcattcag  | tgtgggccct  | 1260 |
| caggcagccc  | tgaagcctgg | ctgggtcatc  | agatgggggc  | agcctgtgac  | gggcaccagc  | 1320 |
| ggcctgatcc  | cagggaagag | ttcctggagg  | gtgttggtctg | tttttggttag | ctcagttttt  | 1380 |
| ttctgggctc  | caccattcct | aactccaggt  | agacaagata  | gatgtcacac  | acaacaattt  | 1440 |
| taaagtattt  | tgcttagtgc | attttgttta  | tgattgcagt  | gtttgtttct  | tatttaatatg | 1500 |
| gctttttact  | tcattctatt | aaatttttagt | gtttagaaga  | ggcgggtact  | gtcactgtgt  | 1560 |
| aaaatatgta  | atattttata | tggtataacca | tgatcatatat | acttgcaata  | tcagaccttg  | 1620 |
| cattcaatat  | acaatgcaat | tgactctttg  | cagacctgca  | tttttcagtg  | aacaataaaa  | 1680 |
| agattgtctg  | gcactccaaa | aaaaaaaaaa  | aaaaaaaaaa  |             |             | 1720 |

&lt;210&gt; 134

&lt;211&gt; 705

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (349)

&lt;223&gt; n equals a,t,g,.or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (409)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 134

|             |            |            |             |            |             |     |
|-------------|------------|------------|-------------|------------|-------------|-----|
| ggcagcaggc  | catctgggct | cattcagcag | gaaataatgg  | aaaaagctgc | aatatccagg  | 60  |
| tgtttactac  | aatctggagg | caagatcttt | cctcagtatg  | tgctgatgtt | tggttgctt   | 120 |
| gtggaatcac  | agacactcct | agaggagaat | gctgttcaag  | gaacagaacg | tactcttgga  | 180 |
| ttaaataatag | caccttttat | taaccagttt | caggtaccta  | tacgtgtatt | tttggaacct  | 240 |
| tcctcattgc  | cctgtatacc | tttaagcaag | ccagtgggaa  | tcttaagact | agatttaattg | 300 |
| actccgtatt  | tgaacacctc | taacagagaa | gtaaagggtat | acgtttgtna | aatctgggaa  | 360 |
| gacttgactg  | ctattccatt | ttgggtatca | tatgtacctt  | gatgaagang | attagggttg  | 420 |
| gatacttcaa  | gtgaagcctc | ccactggaaa | caagctgcag  | ttgttttaga | taatcccatc  | 480 |
| caggttgaaa  | tgggagagga | acttgtactc | agcattcagc  | atcacaaaag | caatgtcagc  | 540 |
| atcacagtaa  | agcaatgaag | agcagttttc | caatgaaaac  | tgtgtaaata | gagcatcaac  | 600 |
| aagtacaaaa  | ttcttgtctt | aattagtggg | ggtatataaa  | aattccttgt | aatgggtcaaa | 660 |
| tattttttta  | aattgacatt | aataaagcat | attttaaaag  | tttct      |             | 705 |

&lt;210&gt; 135

&lt;211&gt; 323

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 135

|             |             |            |             |            |            |     |
|-------------|-------------|------------|-------------|------------|------------|-----|
| agcacacacc  | tccttttagtt | gctcctaagg | tcattgttcaa | cattcgtgga | gtgcattttc | 60  |
| tgctcaggga  | gctttcccag  | acccggaatg | tttggtgctc  | acagacyctg | gcaaggatcg | 120 |
| gtattgctgt  | tcctcagttt  | tgcttgggga | aatggaggst  | cagtgcaggt | cagtgcagtg | 180 |
| cccagagtca  | tgccattggc  | gggtggccca | gkgmtccagg  | tctccagcac | ccctcggccc | 240 |
| cctcctcacc  | aggtcacatc  | atctcctgga | ttagaatctg  | ctcacatagt | ctgtcctgaa | 300 |
| aggaaaaaaaa | aaaaaaaaaa  | aac        |             |            |            | 323 |

&lt;210&gt; 136

&lt;211&gt; 582

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 136

|            |             |            |            |            |            |     |
|------------|-------------|------------|------------|------------|------------|-----|
| ggacggaatg | gtgcaaccct  | cctwamtttt | ctkgkgctgt | tgacaacaga | gggagggagg | 60  |
| gaaaacatct | ttygtgggag  | aatcctacyt | ctgcagsgga | gcccttaagc | gatkgtttt  | 120 |
| gaatctkgac | cctttaccaa  | ctaattttga | aggaagatac | cttggaata  | tttggcatc  | 180 |
| agtgggttac | tgaaacagca  | ttagtgaatt | catctagaga | actctttcat | ttattcaggc | 240 |
| aacaactgta | caacttggaa  | accttgttac | agtccagttg | tgattttggg | aargtatcaa | 300 |
| ctctacactg | caaagcagac  | aatattaggg | agcagtgtgt | actatttctc | cattatgtta | 360 |
| aagttttcat | cttcagggtat | ctgaaaagta | agaatgctga | gagtcaggtt | cctgtccatc | 420 |
| cttatgaggc | tttggaggct  | cagcttcctc | cagtgttgat | tgatgagctt | catggattac | 480 |
| tcttgatat  | tggacaccta  | tctgaacttc | ccagtgttaa | tataggagca | tttgtaaatc | 540 |
| aaaaccagat | taaggtttga  | ctggtttcat | ttgattttta | ag         |            | 582 |

&lt;210&gt; 137

&lt;211&gt; 1021

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

<222> (248)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1004)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1014)  
 <223> n equals a,t,g, or c

<400> 137  
 ttccggcagag cccttgccgag ctcttgaata cctgckttct gtagcgctag ttctcttcaa 60  
 gatttgctta gtgtcatttc atttcggttt cttttctcgc catgtttttc tgtcggaaatt 120  
 acgggttcgtt ttggttctat gtactctcta aaatgttatc gtttttcatt tgtctactaa 180  
 ttttcgtgca tttgttacta ctgagtttct taatatctga ctggcctccg cccacgggct 240  
 ctgcaganca taaaatactc aggctgatgg tagtgcagag actctccctc cttgatcagc 300  
 gcaaacgttg gtctgaggct tgagggatgg agcaacattt tcttggtgt gtgaagcggg 360  
 cttgggattc cgcagaggct ggcgcagagc cccagcctcc acctattgtg agttcagaag 420  
 atcgtgggcc gtggcctctt cctttgtatc cagtactagg agagtactca ctggacagct 480  
 gtgatttggtg actgctttcc agcccttgct ggcggctgcc cggagtctac tggcaaacg 540  
 gactctctcc tggagtccag agcaccttgg aaccaagtac agcgaagccc actgagttca 600  
 gttggccggg gacacagaag cagcaagarg caccgcgtaga akargtgagg caggcagarg 660  
 aacccgacag actcaggctc crgcagcttc cctggagcag tcctctccat ccytgggaca 720  
 gacagcagga caccgaggct tgtgacagcg ggtgcctttt ggaacgcgc catcctcctg 780  
 ccctccagcc gtggcgccac ctcccgggtt tctcagactg cctggagtgg attcttcgcg 840  
 ttggttttgc cgcgttctct gtactctggg cgtgctgttc acggatctgt ggagctaagc 900  
 agccttagat agcagcagaa ggcttttttg attctcctcc ttgaaaagat tctcagttac 960  
 caaacgtctc cacctagaaa ataaaaatac attaagatgt tganaaaaaa aaanaaaaaa 1020  
 a 1021

<210> 138  
 <211> 1777  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (118)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (237)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (661)  
 <223> n equals a,t,g, or c

&lt;400&gt; 138

|             |            |             |            |            |             |      |
|-------------|------------|-------------|------------|------------|-------------|------|
| gattgtttac  | gatcatatcc | ggcgatttgg  | gtaccggggc | cccccccgac | tttttaantt  | 60   |
| ttttttttgc  | gagacagggg | ctcactttgt  | ggctcaggct | ggagtgtact | ggcacgtnct  | 120  |
| tagctcactg  | cagccttgaa | ctcctgggct  | caggcaatcc | tcctacctta | gcctcctgag  | 180  |
| tagctaggac  | tacaggaatg | tgccatcatg  | cctgggcta  | ttttaagttt | tttgtanaga  | 240  |
| tgggatctca  | ctatgttgcc | caagctgggt  | tcagattcct | gtgctcaagg | gattctgcta  | 300  |
| acttggctcc  | ccaaagtgt  | gggattacaa  | atgtgagcca | ctgtatctgg | cccatattct  | 360  |
| tttttaagaa  | aaagatgcag | aggtgttaaa  | tattaatatc | aaattgtcca | ggcatgggtg  | 420  |
| ttatgaaatt  | gtgtgccctc | tgacaggcaa  | ccaaacacac | acgacttcat | ttctttatta  | 480  |
| attcctgcct  | catcatcttt | tctcattgat  | gctccttaat | gtcaaaggaa | tctctctctc  | 540  |
| tcacacacac  | ataagaccaa | aacaaatata  | ttgaacatgc | aaaaaaatag | tctacgcttt  | 600  |
| tgaatagtgt  | gcactgttga | atagtgtgca  | ctgttggata | gtgtgcactg | ttgaagtgtg  | 660  |
| natgtgccta  | aggcaacagg | atcttgggaa  | agctctagat | ttttggcytc | gaaataaaac  | 720  |
| tgcattgtga  | atagcagggt | tttacattta  | ttattgttgt | gtatttcttc | ccctttttgc  | 780  |
| aatactatct  | acgctgagtt | atctattgcc  | aactagcacc | aattctccaa | atcaaagtgt  | 840  |
| gtgagggaaa  | cacactcgtg | caatcctctt  | taacagaaga | tacaccaagt | aacctgtctg  | 900  |
| tctacttctg  | ttaccagaaa | ataaaaagaac | ttgaagggtc | gcttggctgg | aggggtccgg  | 960  |
| gtgggagagc  | atcctgccct | cagtcggaat  | ccatggtgaa | cagctggatg | tcctgtggat  | 1020 |
| tccagtacag  | gccgactgct | gagttgtaga  | caagagacca | gacatagggg | ataaaaaact  | 1080 |
| cctcgggctg  | ctcctcttcc | acataattga  | atttcaattc | tggaaatttc | ttcagtctgt  | 1140 |
| ctttgggcag  | cgcaacgcag | ccttgcttaa  | tgatttccag | gacccgttcc | actgacagct  | 1200 |
| cagctcccag  | cttgagcaga | ccttgagcta  | aagaaggaga | tcaccagatc | aatattttgc  | 1260 |
| attatatcct  | gaaatgaagg | atgagttcga  | aattgttcaa | agagatcgcg | tttgtaaagc  | 1320 |
| agggcgatata | ccaagtttgg | gttgtggtga  | agggaaattg | tcaggcagga | gttgatgatc  | 1380 |
| tctaactaca  | ttcgaatcac | ttcttcaatg  | acatttaggt | cttgtgcata | atctggtaga  | 1440 |
| ggaacatcat  | tagaactcag | cgaacctctc  | aaggactgtg | tggcttggtc | cagaactttg  | 1500 |
| ttgtgttttt  | tagacagcaa | agaaaaataaa | ctgatgatcc | tctgggcagc | atactatggg  | 1560 |
| agagaacgaa  | actgtgccga | catattttgt  | aaagctgcca | aacaatttgt | gtgaaggtac  | 1620 |
| ttgtctcgtg  | tcctagtcag | gttgtattga  | atggttctta | ttaccaccag | gatcaggaga  | 1680 |
| ctccccaaag  | agatttccag | taaaactcgt  | tctgaatacc | aagtaatatt | tttttagtatc | 1740 |
| acttcatgaa  | tggatctgtt | gaagccatca  | tcttccg    |            |             | 1777 |

&lt;210&gt; 139

&lt;211&gt; 643

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 139

|            |            |            |             |             |             |     |
|------------|------------|------------|-------------|-------------|-------------|-----|
| tttttttttt | tttttttttt | tttttttttt | ttttttttggg | aatgagaaaa  | taacttttatt | 60  |
| ttcattgttg | ggagcggggc | gatgtccagc | ctcagaactt  | ctggaactgc  | ttcttgggtg  | 120 |
| cggcagcctt | ggtgaccttg | agcacgttga | agcgcactgt  | cttgctcaga  | ggccggcact  | 180 |
| cgccactgtg | gacgatgtca | ccgatctgga | cgtccctgaa  | gcaggggggac | aggtgtacag  | 240 |
| acatgttctt | gtggcgcttc | tcgaagcggg | tgtacttgcg  | gatgtagtgc  | agatagtctc  | 300 |
| ggcggatgac | aatggtcctc | tgcatcttca | tcttgggtca  | ccacgccaga  | gaggatccgc  | 360 |
| cctcgaatgg | acacattacc | agtgaagggg | catttcttgt  | caatgtaggt  | gcccctcaat  | 420 |
| agcctccttg | gggtgtcttt | gaagcccaga | ccgatgttct  | tgtagtaaac  | ccgcgggagc  | 480 |
| ttctccttgc | cagtttctcc | cagcaggacc | ctcttcttgt  | tttgaaagat  | ggtcgggtgc  | 540 |
| ttttggtagg | cacgctcagt | ctgaatgtcc | gccatcttct  | cgtgccgmay  | tcctgcagcc  | 600 |
| cgggggatcc | actagttcta | gagcggccgc | accgcgggtg  | agc         |             | 643 |

&lt;210&gt; 140

&lt;211&gt; 1220

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
 <221> SITE  
 <222> (404)  
 <223> n equals a,t,g, or c

<400> 140  
 tttttttttt ttgagatgga atcttgtctct tgttgtccag gctggagtgc aatggcacga 60  
 tcctggctca ctgcaacctc tgccctcctag cttcaagggg ttctcctgcc tcagcctccc 120  
 gagtagctgg gattacacgt gccaccacc acgccgact aatattkgta tttttagtag 180  
 agacggggct tcaccagggt gccaggcta gtcttggaa tcctgacytc gtgatccacc 240  
 tgcytcggcy tcccaaagtg ctgggattac aggtgtgagc cgtcttgtgt tttttgtttt 300  
 tgtttgtttt taaaagatgg artttcactc ttattgcccs ggctggaktg caatggcacr 360  
 atctcggctc accgcaatct ccacctcctg ggctcaagca attnttctgc cccagcctcc 420  
 caaagtgtcg gaattacagg tgcccgccac catgcccaac caattttcsg taytcytagt 480  
 agaggtgggg ttccacaacg tkggccaggc tggtytcaa ctcaaaytcc tgacytcagg 540  
 tgatctgccc actttggcyt cccgaaatgc tgagactaga ggcgcgagcc accacgcctg 600  
 gcctacaaac acattcttgt ttgggttttt atataaaata tgagcacaaa aatactttcc 660  
 ctaaatacag cctctggcct tgccctaacc ttggcacaca sccaagtacc tcttccattc 720  
 tcagatagct gaggggagtg tatagagggt tagagtacat acgtttcttc tccaactctt 780  
 cgctgcttag aagaagacta accacctctt tgggtttcaa ggtatctggt ttgaagttcc 840  
 cacctgaaat caccatccgc tgaatctcac tcttctcctt ggctctttgc agaatgcgtt 900  
 cttcaatggt gcctttacag atgagccggt acacagtaac ctgctttgtc tgccctaagc 960  
 ggtgggccct gtccatggcc tgctggtcca cagtggggtt ccagtcgcta tcatagaaaa 1020  
 tgcactgtgt ctkcagcagt gagattgata cccagtcctc cagctcgtgt gcttaacagg 1080  
 aacacaaaga tgtcattcct gttctgaaaa tcagcaacca tgtctcgctc ctccgagatc 1140  
 ttggatgagc catcaagcct yatgtaggta tgcttctctg aaaccatgta ttcctccagt 1200  
 aggtctatca tcctcgtgcc 1220

<210> 141  
 <211> 721  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (623)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (626)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (638)  
 <223> n equals a,t,g, or c

<400> 141  
 aattcggcac gagccagggt agccggaagg gcagctctcc aggccctgcc caccacacag 60  
 ggggctcctt atgcacagcg gggcgtctcc ttgtggccat agaaacggaa ctggctcttt 120  
 tcaacagtgc tgcaagagga tggttattta acgctggccc ccaaggagga aaggcacaga 180  
 cyttcctccc tcctggaaca tccaagggca ctggatcctc tgtgtccctc tgagatgggg 240  
 tgccactcca gcaagagcac cacgggtggca gctgagtcct agaagcttga agaagagygc 300  
 gagggaagag agccaggctc ggagaccggc acccaggcag cagactgcaa ggatgccccg 360  
 ctgaaggatg gaacccttga gccaaagagc tgaaatgcct ctctccagag tcggaccctc 420  
 acctcyttcc tggaaactgcc tttggcccca gaaccatgag acaatcccca ccctgagaag 480

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ctccgatcac | tgggaggaga | gagaaagcct | ccagcttttg | gattcagggt | tcagaagttt | 540 |
| ttagcagcct | ttgctcattg | gagaggtggg | gaaaggataa | agttcttata | aggaaatccc | 600 |
| taatttcccc | cagctcctcc | ccnccngaag | aaggaacnaa | agaaagttcc | ttccacacgt | 660 |
| tttggtggaa | acttttccct | tgccaacttt | ccttggttg  | ccagaacaaa | gccctccaga | 720 |
| a          |            |            |            |            |            | 721 |

&lt;210&gt; 142

&lt;211&gt; 1468

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (901)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 142

|             |             |            |            |            |             |      |
|-------------|-------------|------------|------------|------------|-------------|------|
| atgaattaat  | gtttataaat  | gactgtactg | aattttaaac | cgtacagttt | catttgcatt  | 60   |
| ttgacattac  | tttattatac  | attttgcatt | taaaaggctg | caccagttgg | cttttcttct  | 120  |
| gttttattct  | caaaatatag  | agattctgtg | atttatttgc | cctgtttatg | gattaaaaag  | 180  |
| aaaattctaa  | tataaagcat  | ttcaatagga | tgcataggta | tattacgttt | tttaaagtct  | 240  |
| ttagatctgt  | gattcttgac  | ttactattta | ttttatcccc | tttaagtcag | ggatgcttta  | 300  |
| ttctatttta  | aagcacttat  | gagttacatg | ttgtaatcaa | gtttgcacaa | tatatattatc | 360  |
| tatatgagga  | acccataaat  | gaatagctaa | ttttttaa   | gccattaaaa | tgcatgaaat  | 420  |
| kcttatttaa  | accttactat  | actatttctt | caaggcaagt | aaattgacca | tgrgraaagr  | 480  |
| acacagttat  | taaacactgt  | tgacaggaaa | attctccttg | ataacatagg | acaattaatg  | 540  |
| gaaaaaaaa   | ttctcattat  | ttgcaaagaa | tgaacaagtt | aatgaacaaa | caaactagat  | 600  |
| ttggtatggt  | ttcagctttt  | gtatcatggt | taattgttta | atgtggttga | aaaactgcag  | 660  |
| ttgagaaatc  | agatagcaat  | atagacattc | acagcagctc | tgtggatacc | atgtaattgt  | 720  |
| caggtaattt  | cagaatgttg  | aaaattattc | agtgcagccc | tcatagtatc | atacttgaag  | 780  |
| aaattgatta  | cagttccact  | aaattgttga | agataaatta | tttttaaagg | ttatgaaaac  | 840  |
| taagtatat   | taattcatat  | gtttgatttt | taaatcccac | ctcctcaagc | tatccaattt  | 900  |
| nctgactttg  | aaaataacca  | tgagagatgc | cacatttctc | tctgggaaac | taccactcaa  | 960  |
| agaataattg  | ttaaaaatta  | agcttttagg | tattagaagc | tgttataaag | tataaaatta  | 1020 |
| agatataagc  | agatcacatg  | taaatcattc | ctaaagcaca | agaaaagaat | gtgccttgat  | 1080 |
| gtacatatat  | tactaagttg  | cctctcccag | tttactttta | aaatggcttt | aaggataaag  | 1140 |
| aataaatgtg  | atagctgtgc  | atgcattata | tatttgcatt | tgcaaatttc | ccattgtttt  | 1200 |
| aacagctgtg  | tggctgactt  | tcaattttta | gacgtgaatt | gacatacagc | ccataacttt  | 1260 |
| ataatggctg  | ctcattttatc | ttatctttca | gttagtggaa | aaacatttca | acctgactaa  | 1320 |
| aattttggaat | tgtgtctttt  | atgttccatc | ctctgttggt | actagattta | gtttaaaaat  | 1380 |
| tgtgtatgac  | cattaatgta  | tgtcataaac | atgtaaataa | aagatgttga | atcttgttga  | 1440 |
| aaagcawraa  | aaaaaaaaaa  | aaactcga   |            |            |             | 1468 |

&lt;210&gt; 143

&lt;211&gt; 300

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (268)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (284)

<223> n equals a,t,g, or c

<400> 143

|             |            |            |             |            |            |     |
|-------------|------------|------------|-------------|------------|------------|-----|
| tgaattttttt | gccaaactta | gtaactctgt | taaatatttg  | gaggatttaa | agaacatccc | 60  |
| agtttgaatt  | catttcaaac | tttttaaatt | ttttgtact   | atgtttggtt | ttattttcct | 120 |
| tctgttaatc  | ttttgtattc | rcctatgctc | tcgtacattg  | agtactttta | ttccaaaact | 180 |
| agtgggtttt  | ctctactgga | aattttcaat | aaacctgtca  | ttattgctta | ctttgattaa | 240 |
| aaaaaaaaaa  | aaaaaaaaaa | aaaccccnag | ggggggggccg | ggtncccaat | cccccccaaa | 300 |

<210> 144

<211> 2243

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (929)

<223> n equals a,t,g, or c

<400> 144

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| tgccctccctt | cctgcagatt  | gtggacagta  | gttcctcagc  | ctgcaccctg  | gattccttct  | 60   |
| tcccttctct  | agctccatgg  | gactcgcccc  | aagactgtgg  | cttcaaggac  | caccagcccc  | 120  |
| ttactcttca  | agccctgact  | gtggagttgg  | tagatgcctc  | tgatcctcag  | tattctctct  | 180  |
| ggcaatgttc  | cacggcttct  | ccttcctggg  | agctggctcc  | ataacttgat  | tttcccaaaa  | 240  |
| cgtgttgcaa  | tccttctgtc  | cccttagcca  | cccagggtct  | tgtgtgggta  | tgagtgtaga  | 300  |
| ggatgggggt  | atgccaggcc  | tgggcccgtc  | caggcaggcc  | cgctggaccc  | tgatgtact   | 360  |
| cctatccact  | gccatgtacg  | gtgcccagtc  | cccattgctg  | gcactgtgcc  | atgtggacgg  | 420  |
| ccgagtgcct  | ttycggccct  | cctcagccgt  | gctgctgact  | gagctgacca  | agctactgtt  | 480  |
| atgcgccttc  | tccttctgtg  | taggctggca  | agcatggccc  | caggggcccc  | caccctggcg  | 540  |
| ccaggctgct  | cccttcgcac  | tatcagccct  | gctctatggc  | gctaacaaca  | acctggtgat  | 600  |
| ctatcttcag  | cgttacatgg  | acccagcac   | ctaccagggtg | ctgagtaatc  | tcaagattgg  | 660  |
| aagcacagct  | gtgctctact  | gcctctgcct  | ccggcacccg  | ctctctgtgc  | gtcaggggtt  | 720  |
| agcgctgctg  | ctgctgatgg  | ctgcgggagc  | ctgctatgca  | gcagggggcc  | ttcaagttcc  | 780  |
| cgggaacacc  | cttcccagtc  | cccctccagc  | agctgtgtgc  | agccccatgc  | ccctgcatat  | 840  |
| cactccgcta  | ggcctgctgc  | tctcattctc  | gtactgcctc  | atctcagggt  | tgctgtcagt  | 900  |
| gtacacagag  | gtgctcatga  | agcgacagng  | gctgcccctg  | gcacttcaga  | acctcttctc  | 960  |
| ctacactttt  | ggtgtgcttc  | tgaatctagg  | tctgcatgct  | ggcgggcggt  | ctggcccagg  | 1020 |
| sctcctggaa  | ggtttctcag  | gatgggcagc  | actcgtgggtg | ctgagccagg  | cactaaatgg  | 1080 |
| actgctcatg  | tctgctgtca  | tgaagcatgg  | cagcagcatc  | acacgcctct  | ttgtgggtgtc | 1140 |
| ctgctcgctg  | gtggtcaacg  | ccgtgctctc  | agcagtcctg  | ctacggctgc  | agctcacagc  | 1200 |
| cgccttcttc  | ctggccacat  | tgtcatttgg  | cctggccatg  | cgctgtact   | atggcagccg  | 1260 |
| ctagtccctg  | acaacttcca  | ccctgattcc  | ggacctgtga  | gattgggcgc  | caccaccaga  | 1320 |
| tccccctccc  | aggccttctc  | ccctctccca  | tcagcagccc  | tgtaacaagt  | gccttgtgag  | 1380 |
| aaaagctgga  | gaagtgaggg  | cagccagggtt | attctctgga  | ggttgggtgga | tgaaggggta  | 1440 |
| cccctaggag  | atgtgaagtg  | tgggtttggt  | taaggaaatg  | cttaccatcc  | cccccccca   | 1500 |
| accaagtctc  | tccagactaa  | agaattaagg  | taacatcaat  | acctaggcct  | gagaaataac  | 1560 |
| cccctccttg  | ttgggcagct  | ccctgctttg  | tcttgcataa  | acagagttga  | tgaaagtggg  | 1620 |
| gtgtgggcaa  | caagtggctt  | tccttgccca  | ctttagtcac  | ccagcagagc  | cactggagct  | 1680 |
| ggctagtcca  | gcccagccat  | ggtgcatgac  | tcttccataa  | gggatccctc  | cccttccact  | 1740 |
| ttcatgcaag  | aaggcccagt  | tgccacagat  | tatacaacca  | ttaccctaac  | cactctgaca  | 1800 |
| gtctcctcca  | gttccagcaa  | tgccctagaga | catgctccct  | gccctctcca  | cagtgtgtgt  | 1860 |
| ccccacacct  | agcctttgtt  | ctggaaaccc  | cagagagggc  | tgggcttgac  | tcatctcagg  | 1920 |
| gaatgtagcc  | cctgggcccct | ggcttaagcc  | gacactcctg  | acctctctgt  | tcaccttgag  | 1980 |
| ggctgtcttg  | aagcccgtca  | cccactctga  | ggctcctagg  | aggtaccatg  | cttcccactc  | 2040 |
| tggggcctgc  | ccctgcctag  | cagtctccca  | gtcccaacca  | gcctggggaa  | gctctgcaca  | 2100 |
| gagtgacctg  | agaccaggta  | caggaaacct  | gtagctcaat  | cagtgtctct  | wtactgcat   | 2160 |
| aagcaataag  | atcttaataa  | agtcttctag  | gctgtagggt  | ggttccctaca | accacagcca  | 2220 |

aaaaaaaaaa aaaaaaactc gag

2243

<210> 145  
 <211> 1082  
 <212> DNA  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (265)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (354)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1064)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1081)  
 <223> n equals a,t,g, or c

|             |             |             |             |             |             |  |      |
|-------------|-------------|-------------|-------------|-------------|-------------|--|------|
| <400> 145   |             |             |             |             |             |  |      |
| gccaaagctct | aatacgactc  | actatagggg  | aagctgggtac | gcctgcagkt  | accgggttcgg |  | 60   |
| ggaattcccg  | ggtcgaccca  | cgcgtccgct  | tccgtgtgtc  | aaaatcctca  | cctccttcat  |  | 120  |
| aaccatctcc  | cacaattaat  | tcttgactat  | ataaatttat  | ggtttgataa  | tattatcaat  |  | 180  |
| ttgtaatcaa  | ttgagatttc  | tttagtgctt  | gcttttctgt  | gactcaactg  | cccagacacc  |  | 240  |
| tcattgtact  | tgaaaaactgg | aacancttgg  | gaatgccatg  | gggtttgata  | atctgccagg  |  | 300  |
| gacatgaaga  | ggctcagctt  | cctggggacca | tgactttggc  | tcagctgata  | ctgnacatgg  |  | 360  |
| gagaacaacc  | acatttttct  | ttgtgtgtgc  | ttctagcagc  | tgttcggggag | gaccktgacc  |  | 420  |
| caayagtgtt  | cccattgctgt | ttcttgtgaa  | atgctctcgg  | ctatgtagca  | gcttttgatt  |  | 480  |
| cctgcatac   | cctaggctgc  | tgccctatc   | ctgtcccttg  | tttataacat  | tgagaggttt  |  | 540  |
| tctagggcac  | atactgagtg  | agagcagtg   | tgagaagtcg  | gggaaaatgg  | tgactacttt  |  | 600  |
| tagagcaagg  | ctgggcatca  | gcacctgtcc  | agctctactt  | gtgtgatgtt  | tcaggaactc  |  | 660  |
| agcccctttt  | tctgcctagg  | ataaggagct  | gaaagattaa  | cttggatcty  | ctaattggtcc |  | 720  |
| aaatcttttg  | gtcacaataa  | agagtctcca  | aattagagac  | tgcatgttag  | ttctggatgg  |  | 780  |
| atttggtggc  | ctgacatgat  | accctgccag  | ctgtgagggg  | accccgtttt  | taagatgcat  |  | 840  |
| ggccaagctc  | tctgcaaagt  | gaaatgctta  | cactgggtgt  | tggggatgtt  | tgctacctcc  |  | 900  |
| tgctattttt  | gtgggttttg  | ttctcccact  | atggtaggac  | ccctggccag  | cattgtggct  |  | 960  |
| tgctcatgtc  | gccccattga  | ctaccttctc  | atgctctgag  | gtactactgc  | ctctgcagca  |  | 1020 |
| caaatttcta  | tttctgtcaa  | taaaaggaga  | tgaaaataaa  | aaanaaaaaa  | aaaaaactcg  |  | 1080 |
| ng          |             |             |             |             |             |  | 1082 |

<210> 146  
 <211> 4313  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1126)



<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (4015)

<223> n equals a,t,g, or c

<400> 146

|             |            |            |             |            |            |      |
|-------------|------------|------------|-------------|------------|------------|------|
| caagctgggt  | tgaactagg  | ggcgggctc  | ggcgcgcgc   | gttggttgc  | gccgcaccc  | 60   |
| cgcttcggg   | ttaggccgt  | cctgcccgc  | ccctcctct   | ctcccttcg  | acccatagat | 120  |
| ctcaggctc   | gctccccgc  | cgccgcagc  | cactgttgac  | ccggcccgta | ctgcggcccc | 180  |
| gtggccacca  | tgtccctgca | cggcaaacg  | aaggagatct  | acaagtatga | agcgccctgg | 240  |
| acagtctacg  | cgtgaactg  | gagtgcgcg  | cccagataag  | gctttcgctt | ggcgctgggc | 300  |
| agcttcgtg   | aggagtacaa | caacaagggt | cagcttggtg  | gtttagatga | ggagagttca | 360  |
| gagtttattt  | gcagaaacac | ctttgaccac | ccatacccca  | ccacaaagct | catgtggatc | 420  |
| cctgacacaa  | aaggcgtcta | tccagacct  | ctggcaacaa  | gcggtgacta | tctccgtgtg | 480  |
| tggagggttg  | gtgaaacaga | gaccaggtc  | gagtggttgc  | taaacaataa | taagaactct | 540  |
| gattttctgt  | ctcccctgac | ctcctttgac | tggatgagg   | tggatcctta | tcttttaggt | 600  |
| acctcaagca  | ttgatacgac | atgcaccatc | tgggggctgg  | agacagggca | ggtgttaggg | 660  |
| cgagtgaatc  | tcgtgtctgg | ccacgtgaag | accagctga   | tcgcccata  | caaagaggtc | 720  |
| tatgatattg  | catttagccg | ggcgggggt  | ggcagggaca  | tggttgctc  | tgtgggtgct | 780  |
| gatggctcgg  | tgcggatgtt | tgacctccgc | catctagaac  | acagcaccat | catttacgaa | 840  |
| gaccacagc   | atcaccact  | gcttcgcctc | tgctggaaca  | agcaggacc  | taactacctg | 900  |
| gccaccatgg  | ccatggatgg | aatggaggtg | gtgattctag  | atgtccgggt | tcctgcacac | 960  |
| ctgtgcccag  | gttaaacac  | catcgagcat | gtgtcaatgg  | cattgcttgg | gccccacatt | 1020 |
| catcctgcc   | catctgact  | gcagcggatg | accaccaggc  | tctcatctgg | gacatccagc | 1080 |
| aaatgcccc   | agccattgag | gaccctatcc | tggctacac   | agctgnaagg | wgagatcaac | 1140 |
| aatgtgcagt  | gggcatcaac | tcagcccga  | ytgtcgccat  | ctgctacaac | aactgcctgg | 1200 |
| agatactcag  | agtgtagtgt | tgggtggcgt | gtgcccacga  | ggcaggggct | tttgtatttc | 1260 |
| ctgcctctgc  | cccaccccc  | aagtaagaag | aaacatgttt  | ccagtggcca | gtatgtcttt | 1320 |
| cattgctttg  | caccactgt  | taccagaagc | tgctctagga  | gttcctggcc | agtccccca  | 1380 |
| tcgcccctct  | tggcagactc | agtgtgtgt  | ggcgccctct  | cagcccagg  | ctgagtttta | 1440 |
| agattttctc  | tcctttcctc | ttctcctttg | gttctcaat   | taaaaaatgt | gtgtatat   | 1500 |
| gtttgtcagg  | cgttgtgttg | aggagcagtt | cacgcactgg  | ctgtgtctat | tcctctgccc | 1560 |
| aggtgtctct  | gtttgtgtcc | caakgywkkt | tttcatgtct  | cgtccatgtc | catgttcgtg | 1620 |
| ttagcactwa  | cgtgggaaca | aataccaatt | tgtcttttct  | cctagtatca | gtgtgtttta | 1680 |
| caaattttta  | ctttgtatat | ttgttatcta | tcaggcta    | ttttttatga | aaagaatttt | 1740 |
| actctcctgc  | ttcatttctt | tgtcttatag | tcctccctct  | ttgcaccttc | ttctcttccc | 1800 |
| tcagtgcctg  | gagctgttac | tgggcccctg | gccccatgag  | cagtttgcc  | tcttgagcca | 1860 |
| ctgcctgtgt  | agtacatacc | tgaccgggag | tccaaaccac  | cttggtgctc | tgaagtccac | 1920 |
| tgactcatca  | cacctttctt | agcctggctc | ctctcaagg   | cattctgggc | ttgtaaacag | 1980 |
| acataggaag  | cctctgttta | ccctgaagca | ccactgtcca  | gcccattgg  | tcccactggc | 2040 |
| agcatggtag  | agctgagaga | aacaggctct | caggggtacct | gacttgaggg | gaatcgtttc | 2100 |
| atgaagctga  | acttcaagca | tatttccagt | acattctttc  | agagtctgtt | tttccatcca | 2160 |
| aatataagcc  | ccaggccatt | ccacttagtg | tcttttcaat  | gataggcaag | aatgatattc | 2220 |
| gagttgaact  | tcggtgcttc | tgttggttga | gtttactgtg  | cctgggtgga | tattgggcat | 2280 |
| tcttttgatt  | gagtggtctg | aggtgagaga | gtcttcccga  | ggcatcctgt | ctgtgcttcc | 2340 |
| aacctgaac   | aagaccttac | atgagagatg | gactgatgga  | ctgcggcaat | cctgggctgt | 2400 |
| caagtggata  | gatagttaaa | aagcattata | ctgtgggtaa  | tgaaggga   | ggaaaaaaa  | 2460 |
| agaaggaaaa  | ggaattatag | accccagg   | tcagccagtt  | aagagctcta | cccacacctg | 2520 |
| tcaaccctc   | tctccccag  | tttaggttct | gagcagatt   | ggacttgtag | cctgcagttg | 2580 |
| tcttttgact  | tgcaggccgc | agtgtctttc | tgttatgtga  | atgagttcca | tggaggggca | 2640 |
| tatgtgtgat  | tccaccgtta | gatgagccct | tggggcaggc  | agtttgggat | gtgctcttgg | 2700 |
| gggaaagtgt  | gctgtttcct | tgcgctctgc | tcctaccgga  | agtttttaag | tcctcttgaa | 2760 |
| ttgctcatct  | gagattagta | gagtagcagg | cctgaaggat  | gatggttttg | tcctcttttg | 2820 |
| ttctcacctg  | cttgagaagt | aaaacagtaa | ctttgttctt  | ctgggcccct | aagctttttt | 2880 |
| gggttaagtct | tccttttcag | aagtagatgt | catttatatg  | caaaagtcta | gctctttgct | 2940 |
| ttaccatata  | gggacctgtc | ccaaagaaaa | aggctctttt  | tttagccagc | atatttcccc | 3000 |

|            |            |             |             |             |             |      |
|------------|------------|-------------|-------------|-------------|-------------|------|
| ttctaccctt | ttactttgtt | gttctgattt  | taggactctg  | gctggccatg  | tgcttgtggt  | 3060 |
| tgccctcctt | gcatttgcca | ctggatttgc  | actgcacgt   | ttggagatac  | aaagcgagca  | 3120 |
| gttcttggtc | agaaccctcc | tctgcttttc  | attgtgtttg  | ataatgggta  | ctgggtcctt  | 3180 |
| ctctcaagg  | tagcaaggcc | aagctgatgg  | ctgcttgttt  | aggaggccat  | cagttccttc  | 3240 |
| ctgtggagaa | gggtctgaaa | tggaagtcag  | tggtagaagg  | ggctggctctg | ctgggcagg   | 3300 |
| cttacatcca | ctgagttcta | agattccttt  | cctgatctgc  | acctacgcct  | ggctctgtatg | 3360 |
| gtggaatttg | tcagctggaa | ctcagaaaca  | acaacttgaa  | aaaaaaataa  | taattagaac  | 3420 |
| atatttgcat | aagatagcta | tttactctgg  | aaaccaacaa  | cttttgagat  | ttcccttgcc  | 3480 |
| ctgtggacgc | ccagctcctg | tcacccctcc  | ttaggtcctg  | cagtacagtc  | ttcccttgaa  | 3540 |
| tgccaccggg | gaccagggg  | gactccaccc  | ccctaagcaa  | gcacacacat  | actcacagtt  | 3600 |
| gatgagttgc | tggtctttga | gtcccagctc  | tcttaccctc  | cctttactcc  | accagcccga  | 3660 |
| cgaccatga  | ctgaggagg  | gatttctaca  | gtctcaggat  | ttagaaagtc  | tgtaagccat  | 3720 |
| ccatgctcca | gaaagcaccc | atctgttgta  | gttgcaaaaa  | caactctgta  | atttgttgag  | 3780 |
| gttctcaaac | tgacagccag | cgagactggg  | tgaggaggccc | tggtatctgtt | ctccctgact  | 3840 |
| gcgggaggag | cagccactag | gacttttagca | ggaagcccac  | atggaggctc  | cgccaggctg  | 3900 |
| tgcccagct  | ggtgatggcc | cttttgctcc  | tggcagcctg  | aggcacagct  | gcctgtattg  | 3960 |
| tcctcatctg | ttctgactga | aggatggagg  | tgctgaataa  | attaggcctc  | aggcntctac  | 4020 |
| caccagagag | ctggagaatg | ggtccacgtc  | attcaaggac  | ctgaattttt  | tatgctcagg  | 4080 |
| agcattggaa | tcctcttctt | ccaggaggga  | attagcctgc  | aaggtttagga | cttgaagagg  | 4140 |
| gaaggtattt | aataactggg | cgaggatggg  | tgtgtgtggc  | cacacctgta  | atcccagcat  | 4200 |
| tttgggaggc | tgaggtggcc | agatcccaag  | gtcagaagat  | cgagaccatc  | ctggctaaca  | 4260 |
| tggtgaaacc | ccatctctac | taaaaataca  | aaattaaatt  | ggccgggcgt  | gaa         | 4313 |

&lt;210&gt; 147

&lt;211&gt; 1183

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1053)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 147

|            |             |            |             |             |            |      |
|------------|-------------|------------|-------------|-------------|------------|------|
| ggcagagcct | caagctgact  | tggattatgt | ggtccctcaa  | atctaccgac  | acatgcagga | 60   |
| ggagttccgg | ggccgggttag | agaggaccaa | atctcagggt  | ccctgactg   | tggtgtgcta | 120  |
| tcakwygggg | agtgtctact  | cagctgctat | ggtcacagcc  | ctcaccctgt  | tggtcttccc | 180  |
| acttctgctg | ttgcatgcgg  | agcgcatcag | ccttgtgttc  | ctgcttctgt  | ttctgcagag | 240  |
| cttccctctc | ctacatctgc  | ttgctgctgg | gatacccgct  | accaccctg   | gtccttttac | 300  |
| tgtgccatgg | caggcagctc  | cggcttgggc | cctcatggcc  | acacagacct  | tctactccac | 360  |
| aggccaccag | cctgtctttc  | cagccatcca | ttggcatgca  | gccttcgtgg  | gattcccaga | 420  |
| gggtcatggc | tctgtactt   | ggctgcctgc | tttgctagt   | ggagccaaca  | cctttgcctc | 480  |
| ccacctcctc | tttgacagtag | gttgccact  | gtcctgctc   | tggtctttcc  | tgtgtgagag | 540  |
| tcaagggctg | cggaagagac  | agcagcccc  | agggaaatgaa | gctgatgcc   | gagtcagacc | 600  |
| cgaggaggaa | gaggagccac  | tgatggagat | gcggctccgg  | gatgcgcctc  | agcacttcta | 660  |
| tgacgactg  | ctgcagctgg  | gcctcaagta | cctctttatc  | cttggtatct  | agattctggc | 720  |
| ctgtgccttg | gcagcctcca  | tccttcgcag | gcactcatg   | gtctggaaag  | tggttgcccc | 780  |
| taagttcata | tttgaggctg  | tgggcttcat | tgtgagcagc  | gtgggacttc  | tcctgggcat | 840  |
| agctttgggt | atgagagtgg  | atgggtgctg | gagctcctgg  | ttcaggcagc  | tatttctggc | 900  |
| ccagcagagg | tagcctagtc  | tgtgattact | ggcacttggc  | tacagagagt  | gctggagaac | 960  |
| agtgtagcct | ggcctgtaca  | ggtactggat | gatctgcaag  | acaggctcag  | ccatactctt | 1020 |
| actatcatgc | agccaggggc  | cgtgacatc  | tangacttca  | ttattowatr  | attcaggacc | 1080 |
| acagtggagt | atgatcccta  | actcctgatt | tggatgcac   | tgaggggacaa | gggggkcggt | 1140 |
| stccgaagtg | gaataaaaata | ggcgggcgtg | gtgacttgca  | cct         |            | 1183 |

&lt;210&gt; 148

<211> 734  
 <212> DNA  
 <213> Homo sapiens

<400> 148  
 gaattcggca gagtgaagca ttagaatgat tccaacactg ctcttctgca ccatgagacc 60  
 aaccacagggc aagatcccat cccatcacat cagcctacct ccctcctggc tgctggccak 120  
 gatgtcgcca gcattacctt ccactgcctt tctccctggg aagcagcaca gctgagactg 180  
 ggcaccaggc cacctctgtt gggaccacaca ggaaagagtg tggcagcaac tgcmtggctg 240  
 acctttctat cttctctagg ctcaggtaact gctcctccat gcccatggyt gggccgtggg 300  
 gagaagaagc tctcatacgc cttccactc cctctggttt ataggacttc actccctagc 360  
 caacaggaga ggaggcctcc tgggggtttcc ccrrggcagt aggtcaaacg acctcatcac 420  
 agtcttcctt cctcttcaag cgtttcatgt tgaacacagc tctctccrct cccttgtgat 480  
 ttctgagggg caccactgcc arcctcaggc aacatagaga gcctcctgtt ctttctatgc 540  
 ttggtctgac tgagcctaaa gttgagaaaa tgggtgccaa ggccagtgcc agtgtcttgg 600  
 ggcccttttg gctctccctc actctctgag gctccagctg gtcctgggac atgcagccag 660  
 gactgtgagt ctgggcasgt ccaaggcctg caccctcaag aagtggaata aatgtggcct 720  
 ttgcttctat ttaa 734

<210> 149  
 <211> 1405  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (604)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (842)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1079)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1334)  
 <223> n equals a,t,g, or c

<400> 149  
 ggcacagtgg accccagact ccctctccgc ctttctctgc ctggggagac ccactgtgtg 60  
 catggcatca ctgactccca tacctctggc tatcaaaggt ttctgccatg gccaccctgg 120  
 aagsaaacca gagggaggta gacagggaga tcagggtccct tctactctgg ttctgtctct 180  
 gtgaaattgt ctcaggctgg ctgtgtccag arggtccctg gttctctcar ggatgccaaa 240  
 tctacaagaa tctctcctct tccagttcct ataacctctc cttccttttg tctctttaga 300  
 ccttgagta gtagcagcca ggttctttct atctctgggt tagtgcatca tctctggtag 360  
 ctcccttacc caggactttg ggaatggtct ttttgtaata cattctcctc aaataattca 420  
 attttgagtg ttctgtatgt atcctgctgg gaggttgta tatacaaata actgtgcccg, 480  
 ttttagcagag aaggagactg aagctcaggg aggttaagtg tctttctcta ggtcgtattg 540  
 tggagaaagt ggctgactgg ggacttgaat gaggtcccta gtttcatgct cggagggcaa 600  
 agangaatgt ccaattggcc tgagataagc ctctggtaaa atgtactgta cataataggt 660  
 aatcaataaa tgttggtga tgacaaacat gttttctttg ttcattagtt atagtgatta 720

|            |            |             |             |            |            |      |
|------------|------------|-------------|-------------|------------|------------|------|
| tgttctaaat | aactccmaca | aggaartcag  | cacatttggga | atatcawtat | ctttccatga | 780  |
| taatatcttt | ccmyggaaag | awaatgat    | tccmaactgg  | gagtgtcccw | agcaratctg | 840  |
| antctgtgta | ttggccctgg | ggtgggcccag | ccccttagac  | tctatggctc | cattctcttt | 900  |
| gtttacaaaa | ttgagataag | gccttattct  | ctcccaccc   | cacccatcca | tattgttttg | 960  |
| agaataaaat | gagaggatgt | gtgtcaagg   | tgtattttgg  | caatagtctc | tgagccattt | 1020 |
| tctgagcacc | tccatactgt | tgacactcaa  | gtaatatattc | atcagcattc | cattcaggnt | 1080 |
| cctcccttaa | tgagggtgtg | gatgtacaag  | agtygtgagg  | tggcaaagga | tgggctcctg | 1140 |
| aggaaacact | taggaaactg | ggctttctgc  | cattaaaaga  | gacaaacctt | tgtggtgacc | 1200 |
| taattaaagt | ttttaaaatt | caatttggaa  | agttagcaag  | ctagctcctk | tccaggwaaa | 1260 |
| ataaggagtc | agtgcattgc | ctaaccgggc  | ccgggctgct  | tgccattcca | aacaactgca | 1320 |
| gtaagtttat | cacnttcttt | cagggactga  | ggtttccagg  | cacagacttg | gataaggaag | 1380 |
| gatgtcctat | ggggtcacat | tgatg       |             |            |            | 1405 |

&lt;210&gt; 150

&lt;211&gt; 2890

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 150

|            |            |            |             |             |            |      |
|------------|------------|------------|-------------|-------------|------------|------|
| ttatatgcta | cagctacagt | aatttcttct | ccaagcacag  | agganctttc  | ccaggatcag | 60   |
| ggggatcgcg | cgtcacttga | tgctgctgac | agtggctcgtg | ggagctggac  | gtcatgctca | 120  |
| agtggctccc | atgataatat | acagacgac  | cagcaccaga  | gaagctggga  | gactcttcca | 180  |
| ttcgggcata | ctcactttga | ttattcagg  | gatcctgcag  | gtttatgggc  | atcaagcagc | 240  |
| catatggacc | aaattatggt | ttctgatcat | agcaciaaagt | ataacaggca  | aaatcaaagt | 300  |
| agagagagcc | ttgaacaagc | ccagtcccga | gcaagctggg  | cgtcttccac  | aggttactgg | 360  |
| ggagaagact | cagaaggtga | cacaggcaca | ataaagcggg  | gggggtggaaa | ggatgtttcc | 420  |
| attgaagccg | aaagcagtag | cctaactgtc | gtgactacgg  | aagaaaccaa  | gcctgtcccc | 480  |
| atgcctgccc | acatagctgt | ggcatcaagt | actacaaagg  | ggctcattgc  | acgaaaggag | 540  |
| ggcaggtatc | gagagcccc  | geccaccctc | cccggctaca  | ttggaattcc  | cattactgac | 600  |
| tttccagaag | ggcactccca | tccagccagg | aaaccgccc   | actacaacgt  | ggcccttcag | 660  |
| agatcgcgga | tggtcgacag | atcctccgac | acagctgggc  | cttcatccgt  | acagcagcca | 720  |
| catgggcac  | ccaccagcag | caggcctgtg | aacaaacctc  | agtggcataa  | aycgaacgag | 780  |
| tctgaccgcg | gcctcgcccc | ytatcagtc  | caagggtttt  | ccaccgagga  | ggatgaagat | 840  |
| gaacaagttt | ctgctgtttg | aggcacagac | ttttctggaa  | gcagagcgag  | ccacctgaaa | 900  |
| ggagagcaca | agaagacgtc | ctgagcattg | gagccttgga  | actcacattc  | tgaggacggt | 960  |
| ggaccagttt | gcctccttcc | ctgccttaaa | agcagcatgg  | ggsttcttct  | ccccttcttc | 1020 |
| ctttcccttt | tgcatgtgaa | atactgtgaa | gaaattgccc  | tggcactttt  | cagactttgt | 1080 |
| tgcttgaaat | gcacagtgcg | gcaatcttcg | agctcccact  | gttgctgcct  | gccacatcac | 1140 |
| acagtatcat | tccaaattcc | aagatcatca | caacaagatg  | attcactctg  | gctgcacttc | 1200 |
| tcaatgcctg | gaaggatttt | ttttaatctt | ccttttagat  | ttcaatccag  | tcctagcact | 1260 |
| tgatctcatt | gggataatga | gaaaagctag | ccattgaact  | acttggggcc  | tttaaccac  | 1320 |
| caaggaagac | aaagaaaaac | aatgaaatcc | tttgagtaca  | gtgcttgctc  | acttgtttac | 1380 |
| aatgtctccc | ttttaaaaaa | aaaaaaatga | gttttaaagat | ttgttcaga   | gagtaaatat | 1440 |
| atatccattt | aatgattaca | gtattatttt | aaaccttaag  | taggggtggc  | agcctgggtt | 1500 |
| ctgaaaaacc | aaatatgccg | gacaggggtg | ggccacacca  | agaagacggg  | aagacctggc | 1560 |
| ttgtgaccct | ggcttcccat | gtccttctgg | tctcaccgcg  | gaagtgcctc  | atcctggaag | 1620 |
| tatgaaatgt | tagccaatta | ataccaagac | acctcatctg  | ctccttcccc  | agtggatggg | 1680 |
| gttcttctgt | aaaactgttt | gcacatggcc | aggggagggg  | actaggacc   | ttgtgtcctg | 1740 |
| tctggaccct | atggaggcag | gacggtgtca | ttggcgatg   | tgctctgctc  | cattgagatg | 1800 |
| gatggcaaac | cccatTTTTA | agttatat   | ctttgatttt  | tgtaatttta  | gaggtgtagg | 1860 |
| ttttgttttt | tgTTTTTTTg | ttttttttta | agagaaacat  | ttataactgg  | atagcattgc | 1920 |
| agtgaagca  | gcttgggatg | ttggagctaa | tgccagctgt  | ttatactgct  | ctttcaagac | 1980 |

|            |            |             |            |             |            |      |
|------------|------------|-------------|------------|-------------|------------|------|
| agcctccctt | tattgaattg | gcattagggg  | ataaacaagc | ctttaaacgt  | gataaaagat | 2040 |
| caaaaacctg | gtagacatg  | ccagcctttg  | caaggcaggt | tagtcaccaa  | agactaacct | 2100 |
| ccaagtggct | ttatggacgc | tgcataataga | gaaggcctaa | gtgtagcaac  | catctgctca | 2160 |
| cagctgctat | taaccctata | atgactgaaa  | tgacccctcc | actctatttt  | tgtgttgttt | 2220 |
| tgcacagact | ccggaaaagt | gaaggctgcc  | aatctgagta | gtactcaa    | gtgaggaact | 2280 |
| gctggctctg | gatttttttt | ccattaaatt  | cagctgatca | tattgatcag  | tagataaacg | 2340 |
| taaatagctt | caaattttta | aagtgggaatt | gcagtgtttt | ttcactgtat  | caaacaatgt | 2400 |
| cagtgcctta | tttaataatt | ctcttctgta  | tcatggcatt | tgtctacttg  | cttattacat | 2460 |
| tgtcaattat | gcatttgtaa | ttttacatgt  | aatatgcatt | atttgccagt  | tttattatat | 2520 |
| aggctatgga | cctcatgtgc | atatagaag   | acagaaatct | agctctacca  | caagttgcac | 2580 |
| aaatgttatt | taagcattaa | gtaattgtag  | aacataggac | tgctaattct  | agttcgctct | 2640 |
| gtgatgtcaa | gtgcagaatg | tacaattaac  | tggtgatttc | ctcatacttt  | tgatactact | 2700 |
| tgtacctgta | tgtcttttag | aaagacattg  | gtggagtctg | tatccctttt  | gtatttttaa | 2760 |
| tacaataatt | gtacatattg | gttatatttt  | tgttgaagat | ggtagaaatg  | tactatgttt | 2820 |
| atgcttctac | atccagtttg | tacaagctgg  | aaaataaata | aataataacat | aaaaaaaaaa | 2880 |
| aaaaaaaaaa |            |             |            |             |            | 2890 |

&lt;210&gt; 151

&lt;211&gt; 2399

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (128)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (219)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (255)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (272)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2354)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2364)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 151

|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| gaacttttcc  | atctggcaaa  | cgggaaactc  | catccccatt  | aaaccaactc | ccccttttgg  | 60   |
| tttccccccc  | agnggaatag  | aatttggacn  | cccatataaa  | tccaggaaac | cacctaaatt  | 120  |
| ctttagtngt  | ttgtgtttgc  | aagatctaag  | gtcatggtaa  | acattaagtt | cttaaaattt  | 180  |
| ttgggaggga  | ccagtgcacc  | tctccctctg  | aattgttcnc  | caatttaaaa | ttggagtaag  | 240  |
| gttttaaaat  | gtctnattcc  | attggaaggg  | tntgttattt  | cattttgagc | ccagagggga  | 300  |
| gaggcacatt  | ttaaatatca  | gaattagatt  | agctttgagt  | ttgtacaatt | gggaacataa  | 360  |
| tagattttca  | taaattatgt  | gtgccttggt  | ggaagtgtca  | actgtcttta | tgtctgcttg  | 420  |
| taaaagtttc  | aaaatatggt  | ttccctcaaa  | aaggcaacgt  | tacttcattt | gcttgaatat  | 480  |
| tatgatagga  | atgcttactg  | atattacttg  | atagtcatat  | atagcctagg | aaatttaaca  | 540  |
| tatatataac  | tatagcagta  | tttaataatga | tagttgtact  | tctttaaaac | attaaatttg  | 600  |
| aggaaaacttt | aatgctgtct  | cgtgtacatt  | gctttactac  | agtgaggggg | aatatccttt  | 660  |
| agattgagcc  | tcaatttact  | ggttagtagt  | atgtgaactc  | tggtataaaa | acgtaaaacta | 720  |
| gacagtagag  | ccgatgaatt  | aaaattgtta  | attgtctacat | tggcattttc | tacctccttt  | 780  |
| tctgtcagag  | tattactttt  | tccagcattt  | attcttattt  | gtgagtaaag | aggaaatggg  | 840  |
| aacctgaggt  | taaaattgac  | atttttgttt  | cattgagaat  | ttaagcagta | ggtacaggag  | 900  |
| aagtgacttg  | tcacattaat  | ttggtgccta  | aatctgtaac  | tacaagttgt | gatcgacatg  | 960  |
| tacaaaatgt  | ctaagaaagg  | tcatatgctg  | aatattttac  | ttttcctgta | tagtctgcat  | 1020 |
| gatttgtttc  | ataaacccag  | cttatttcct  | ccaaaaagca  | aaatggctct | gtaattttta  | 1080 |
| aagtaaaata  | aacgtgccat  | tttgtctgca  | atctataatt  | tcaggaagtt | attgraagtt  | 1140 |
| ctgactcagg  | gctttttaac  | agttcaagca  | attgtcagtt  | atattttgga | aactccatct  | 1200 |
| gtgtaattct  | ccagtgcctt  | gaaagaatta  | ttacttggc   | aacactatta | aaactttata  | 1260 |
| aaagatggtc  | tttagtgcac  | gtgtatcatt  | atatacacgt  | tttaaagtca | tattgcttag  | 1320 |
| cttgtaataa  | atgattctgc  | atgtgtgctg  | ggtttggtta  | attctttaaa | ggaagttttc  | 1380 |
| tagatttgca  | cttgatgttt  | gttttttaaa  | aactgattat  | ttatggccgt | gacactgtta  | 1440 |
| ccagaaaagt  | aattctaatt  | aagttattat  | gcaaagtcac  | ctataagtag | catctgggaa  | 1500 |
| gaggagatcg  | aggccacagt  | ttgctatttt  | agtatgaaag  | gaggatctgt | ttgggaaaca  | 1560 |
| tagattgtct  | tccctcaaaa  | tgaggggaaa  | aaaaaaagacc | ctttgttcaa | atggattctg  | 1620 |
| ttgtaaaaaa  | ttatttttaa  | aggaaatcac  | aaattgtatg  | tcattcttaa | tgctagtctt  | 1680 |
| atagaataaa  | tccataaaat  | tgtttttatg  | ttcagtatgt  | ttatgtcatt | ctaaatgcag  | 1740 |
| caaattcaat  | gatagcagtt  | caattgactc  | atagcagtg   | tttgtatttt | ttctaattct  | 1800 |
| ttagctttca  | atattggatt  | aaagtcttgt  | ttgtgaatat  | agtttccgta | tggcaaatga  | 1860 |
| tttcttgctt  | attagctttt  | gttaagaat   | gcttagtaag  | agctaagctt | ttaaaagtaa  | 1920 |
| tgcaaacatt  | tatcgtaaat  | aaaacctatg  | gtgtaatatc  | atataatgct | tttctttgat  | 1980 |
| ctttggagaa  | ttattctttt  | atagtagtat  | acatgaattt  | tgatttttaa | agcattttaa  | 2040 |
| aacaaatctc  | aatacattaa  | aaaacctgtt  | attgttaaaa  | rggaaattac | catgccttta  | 2100 |
| agaaacaagg  | atgtacatct  | tcaattcagc  | atragtgtcc  | acatctagaa | ggctctcatt  | 2160 |
| gcagttgttt  | acagtttaagg | tacctctatc  | taaagggcca  | aagaagcatt | tcatayttta  | 2220 |
| acacctcaca  | ttctttcagg  | attaagacat  | atgaaaatag  | tctgaatagg | ataaatttgg  | 2280 |
| ataggaagta  | acttaaccag  | tctgggaaga  | ttcaggcttt  | ttctatkaaa | aagcttattc  | 2340 |
| ctcttcacaa  | ctcnggtggt  | aggntttcat  | ttttcaagag  | ggtagatatt | ttaaagcca   | 2399 |

&lt;210&gt; 152

&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (105)

&lt;223&gt; n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (730)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (755)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (757)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (777)  
 <223> n equals a,t,g, or c

<400> 152  
 cgtgcctgta gtaagctcat ccctgccttt gagatgggtga tgcgtgccaa ggacaatggt 60  
 taccacctgg actgctttgc atgtcagctt tgtaatcaga gattntgtgt tggagacaaa 120  
 tttttcctaa agaataacwt gaycctttgc caracggact acgaggaagg tttaatgaaa 180  
 gaagggttatg caccctmgtt togtgatct atcaacatca ccccatthaag aatacaaaagc 240  
 actacattct tttatctttt ttgctccaca tgtacataag aattgacaca ggaacctact 300  
 gaatagcgta gatataaggaa ggcaggatgg ttatatggaa taaaaggcgg actgcatctg 360  
 tatgtagtga aattgccccca gttcagagtt gaatgtttat tattaaagaa aaaagtaatg 420  
 tacatatggc tggatttttt tgccttgctat tcgtttttgt gtcacttggc atgagatggt 480  
 tattttggac tattgtatat aatgtattgt aatatattgaa gcacaaatgt aatacagttt 540  
 tattgtgtta ccatttgtgt tccatttgct yctttgtatt gttgcattta gtacaatcag 600  
 tgtttaaact tactgtatat ttatgctttc tgtatttacc agctatttta aatgagctgt 660  
 aactttctag taaagaattg aaaagcaaat cctcactaaa ggatacacag gataggataa 720  
 agccaagtcn catcaacatt aaaaaatact aaaaananaaa acacaaaaaa aaaaaanccc 780  
 gggggggggcc cggaacccat tc 802

<210> 153  
 <211> 461  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (77)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (437)  
 <223> n equals a,t,g, or c

<400> 153  
 ctaggagcac cgagcagctt ggctaaaagt aagggtgtcg tgctgatggc cctgtgcgca 60  
 ctgaccgcgc ctctgcncct tctgaacctg gcgccccga ccgtcgccgc ccctgccccg 120  
 agtctgttcc ccgcgcgcca gatgatgaac aatggcctcc tccaacagcc ctctgccttg 180  
 atgttgctcc cctgcgcgcc agttcttact tctgtggccc ttaatgccaa ctttgtgtcc 240  
 tggaagagtc gtaccaagta caccattaca ccagtgaaaga tgaggaagtc tggggggccga 300

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gaccacacag | gtgggaacaa | ggacaggggg | atttaagcag | tcaaaaggaa | aaacatgtta | 360 |
| agaccctaga | cttgtatatt | gacacacttg | taccttgtaa | ggcagaggaa | tgtaattaaa | 420 |
| aagcacttat | ttggcwnaaa | aaaaaaaaaa | aaaaaaaaaa | c          |            | 461 |

&lt;210&gt; 154

&lt;211&gt; 2388

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 154

|             |            |             |             |             |            |      |
|-------------|------------|-------------|-------------|-------------|------------|------|
| gccccgcgt   | ccgaaagcgg | agaacgctgg  | tgggcctggt  | gtggagtacg  | ctttggactg | 60   |
| agaagcatcg  | aggctatagg | acgcagctgt  | tgccatgacg  | gcccaggggg  | gctggtggct | 120  |
| aaccgaggcc  | ggcgcttcaa | gtgggccatt  | gagctaagcg  | ggcctggagg  | aggcagcagg | 180  |
| ggtcgaaagt  | accggggcag | tggccaggga  | gactcgctct  | accagtcggg  | ttacttggac | 240  |
| aagcaagtgc  | ctgataccag | cgtgcaagag  | acagaccgga  | tccctggtgga | gaagcgctgc | 300  |
| tgggacatcg  | ccttgggtcc | cctcaaacag  | attcccatga  | atctcttcat  | catgtacatg | 360  |
| gcaggcaata  | ctatctccat | cttccctact  | atgatggtgt  | gtatgatggc  | ctggcgaccc | 420  |
| attcaggcac  | ttatggccat | ttcagccact  | ttcaagatgt  | tagaaagttc  | aagccagaag | 480  |
| tttcttcagg  | gtttggctca | tctcattggg  | aacctgatgg  | gtttggcatt  | ggctgtttac | 540  |
| aagtgccagt  | ccatgggact | gttacctaca  | catgcatcgg  | attggttagc  | cttcattgag | 600  |
| ccccctgaga  | gaatggagtt | cagtgggtgga | ggactgcttt  | tgtgaacatg  | agaaagcagc | 660  |
| gcttgggtccc | tatgtatttg | ggtcttattt  | acatccttct  | ttaagcccag  | tggtcctca  | 720  |
| gcatactcct  | aaactaatca | cttatgttaa  | aaagaaccaa  | aagactcttt  | tctccatggt | 780  |
| ggggtgacag  | gtcctagaag | gacaatgtgc  | atattacgac  | aaacacaaag  | aaactatacc | 840  |
| ataacccaag  | gctgaaaata | atgtagaaaa  | ctttattttt  | gtttccagta  | cagagcaaaa | 900  |
| caacaacaaa  | aaaacataac | tatgtaaaaa  | agagaataac  | tgctgctaaa  | tcaagaactg | 960  |
| ttgcagcatc  | tcctttcaat | aaattaaatg  | gttgagaaca  | atgcataaaa  | aaagttgcac | 1020 |
| aagttcctta  | ttttccttaa | tattttcactt | ctatttaata  | caagctggga  | cataaaaatt | 1080 |
| ctgttggggg  | tacctggggg | aagatgtgag  | aaactaatgc  | tgaattcagc  | ttatacatga | 1140 |
| tgaaaagaaa  | aaccagacaa | aaggagcaca  | taaatatgca  | tacagtgtaa  | ctgttattat | 1200 |
| tttaataccc  | acgataaggg | atttttgtta  | gcatgtttag  | ggggaacgag  | gattggtggg | 1260 |
| atccttgggg  | ccacaggaat | ctgaggcaac  | ggaagatata  | tagagtgatc  | gtccccctgc | 1320 |
| cgaagggaacc | tggcayctgt | caagcagatg  | ctgcagtcca  | aacttcagct  | tttaagatag | 1380 |
| atagctattg  | aaggcagagg | gtcagcagga  | ggatgtgtat  | ttctaatact  | ccctggtaaa | 1440 |
| gtcataggta  | agactcaaaa | gcgggatctt  | attcaaaaagg | caggatattc  | ctttgttttc | 1500 |
| tgtcttgaaa  | tagccccctc | ccctaagggtg | cattctctca  | agttttcagt  | attgctttat | 1560 |
| ttgcagtgat  | taaaagagat | gagagacttt  | ggagacagac  | aacgtaagca  | acacatacac | 1620 |
| acatgaaata  | ctctagacag | agatgaatat  | aaatctggcc  | taataaccag  | ttttccatgt | 1680 |
| aacagtgatt  | ttgtgtttcg | ggctgaagca  | gtggttatat  | taaaagccac  | taattccctt | 1740 |
| atccctttta  | aagattttta | caattctcca  | accacaaaca  | gcacttctaa  | aactaacttt | 1800 |
| actttctgcc  | cataatttgt | tctacatgga  | aaaaaaaaat  | attacttttg  | ccaggggtgt | 1860 |
| gtgtaaatgt  | ggcagaattc | ctagggcaggc | tgacctttac  | agtatgggcc  | tttaagatac | 1920 |
| tggatcctgg  | ttgggcaaca | agtgtcacgc  | ctgaagtttc  | tgaaaacaaa  | ttagaagact | 1980 |
| gttggcttgg  | ctaattctcg | agttcagggc  | caagtttctg  | tagtcagaat  | gaagaataaa | 2040 |
| attgaaagaa  | aaagggggaa | atgcttatac  | ttggcattaa  | gttgaatgcc  | tcaagtctta | 2100 |
| actatggctt  | tgtagatgag | gcaaaagatt  | tcttagtggt  | aaaatttctt  | caacaggtca | 2160 |
| atgccaatct  | gtatgccatt | ttagtaaagt  | aggtaaggag  | agtagccgct  | cagtaacttt | 2220 |
| ggcactaaaag | aaagagtgtg | gctctagaac  | ttccaatccc  | attgctagat  | gtgcccttta | 2280 |
| aaagatggtc  | cagtgccttc | agggaaggat  | gttttagccag | ttttcctagt  | atttgttctt | 2340 |
| taagattttt  | tgacctgtgc | ttaataagac  | ggacgcgtgg  | gtcgaccc    |            | 2388 |

&lt;210&gt; 155

&lt;211&gt; 642

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens



<400> 155  
 aaaacagacc atttaaaaac tcagacaaga ttatatattaa tatattaatt actaaaaagg 60  
 cacaagatta cactgaacat attagctact aaaaaggcac tgctaagaca ttcaagcaaa 120  
 tagctattac acactactgc agatttttaca ggtttctaatt tctaacatat gtttgaaaaa 180  
 tccgtgagta ttccaaaaata tatttaataa tggaatatct gcattaatat accatccatg 240  
 tgtttttacc atttgcccta atattgaata tactgtttac ctcacactaa aaagaaaacc 300  
 agaagcccta tttgtgattt tgggagtggg agcttccatt tttgtgtcaa aaatgaatcc 360  
 tgattcctat ggaaatctct gttattaaga tatttcaaga tgagacaaca ctgaagatca 420  
 aattgtgttt agtatcacta tcttctctcc tcgtttctct cttactcctc atcctcccag 480  
 aatctaccag tttatggtag aaagatgggg accttatttg aatgtgtttt tttttttcca 540  
 tgatgtccaa ttttgttgtg ggaaaggatt tggataaaat ttttgtttta attttggtag 600  
 atttttatct atacaaattt aaataaaatt atgttttgtg ag 642

<210> 156

<211> 1251

<212> DNA

<213> Homo sapiens

<400> 156  
 gccgctgccc ctccacggag ttgctgatca tctgggctgt gatccacaaa cccggttctt 60  
 tgtccctcct aatatcaaac agtggattgc cttgctgcag aggggaaact gcacgtttta 120  
 agagaaaata tcacggggccg ctttccacaa tgcagttgct gtagtcatct acaataataa 180  
 atccaaagag gagccagtta ccatgactca tccaggcact gagcatatta ttgctgtcat 240  
 gataacagaa ttgaggggta aggatatttt gagttatctg gagaaaaaca tctctgtaca 300  
 aatgacaata gctgttgga ctcgaatgcc accgaagaac ttcagccgtg gctctctagt 360  
 cttcgtgtca atatccttta ttgttttgat gattatttct tcagcatggc tcatattcta 420  
 cttcattcag aagatcaggt acacaaatgc acgcgacagg aaccagcgtc gtctcggaga 480  
 tgcagccaag aaagccatca gtaaattgac aaccaggaca gtaaagaagg gtgacaagga 540  
 aactgaccca gactttgatc attgtgcagt ctgcatagag agctataagc agaatgatgt 600  
 cgtccgaatt ctcccctgca agcatgtttt ccacaaatcc tgcgtggatc cctggccttag 660  
 tgaacattgt acctgtccta tgtgcaaact taatatattg aaggccctgg gaattgtgcc 720  
 gaatttgcca tgtactgata acgtagcatt cgatatggaa aggcacacca gaaccaagc 780  
 tgtaaaccca agatcagccc tcggcgacct cgccggcgac aactcccttg gccttgagcc 840  
 acttogaact tcggggatct cacctcttcc tcaggatggg gagctcactc cgagaacagg 900  
 agaaatcaac attgcagtaa caaaagaatg gtttattatt gccagttttg gcctcctcag 960  
 tgccttcaca ctctgtaca tgatcatcag agccacagct agcttgaatg ctaatgaggt 1020  
 agaatgggtt tgaagaagaa aaaacctgct ttctgactga ttttgccttg aaggaaaaaa 1080  
 gaacctattt ttgtgcatca tttaaccaatc atgccacaca agcatttatt ttagtacat 1140  
 tttatttttt cataaaattg ctaatgccaa agctttgtat taaaagaaat aaataataaa 1200  
 ataaaaaaaa aaaaaccccg gggggggccc ggtccccaat tggccctatg g 1251

<210> 157

<211> 2127

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (312)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1212)

<223> n equals a,t,g, or c

&lt;400&gt; 157

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ccggcgaggag | aggggaagctg | cagcgagagg  | cgcggatctc  | agcgcgaggag | cagtgtcttct | 60   |
| gcggcaggcc  | cctgagggag  | ggagctgtca  | gccaggga    | accgagaaca  | ccatcaccat  | 120  |
| gacaaccagt  | caccagcctc  | aggacagata  | caaagctgtc  | tggcttatct  | tcttcatgct  | 180  |
| gggtctggga  | acgtgtctcc  | cgtggaattt  | tttcatgacg  | gccactcagt  | atttcacaaa  | 240  |
| ccgcctggac  | atgtcccaga  | atgtgtcctt  | ggctactgct  | gaactgagca  | aggacgccc   | 300  |
| ggcgtcagcg  | cncctgcag   | cacccttgcc  | tgagcggaac  | tctctcagt   | ccatcttcaa  | 360  |
| caatgtcatg  | accctatgtg  | ccatgctgcc  | cctgctgtta  | ttcacctacc  | tcaactcctt  | 420  |
| cctgcatcag  | aggatcccc   | agtcctgacg  | gatcctgggc  | agcctgggtg  | ccatcctgct  | 480  |
| ggtgtttctg  | atcactgcca  | tctgtgtgaa  | ggtgcagctg  | gatgtctctg  | ccttctttgt  | 540  |
| catcaccatg  | atcaagatcg  | tgctcattaa  | ttcatttggt  | gccatcctgc  | agggcagcct  | 600  |
| gtttggtctg  | gctggccttc  | tgccctgccag | ctracacggc  | cccatcatg   | agtggccagg  | 660  |
| gcctagcagg  | cttctttgcc  | tccgtggcca  | tgatctgcgc  | tattgccagt  | ggctcggagc  | 720  |
| tatcagaaag  | tgccctcggc  | tactttatca  | cagcctgtgc  | tgtkatcatt  | ttgaccatca  | 780  |
| tctgttacct  | gggcctgcc   | cgcctggaat  | tctaccgcta  | ctaccagcag  | ctcaagcttg  | 840  |
| aaggaccggg  | ggagcaggag  | accaagtgg   | acctcattag  | caaaggagag  | gagccaagag  | 900  |
| caggcaaaga  | ggaatctgga  | gtttcagctc  | ccaactctca  | gccacccaat  | gaaagccact  | 960  |
| ctatcaaagc  | catcctgaaa  | aatatctcag  | tccctggcttt | ctctgtctgc  | ttcatcttca  | 1020 |
| ctatcaccat  | tgggatgttt  | ccagccgtga  | ctgttgaggt  | caagtcacgc  | atcgcaggca  | 1080 |
| gcagcacctg  | ggaacgttac  | ttcattcctg  | tgctctgttt  | cttgactttc  | aatatctttg  | 1140 |
| actggttggg  | ccggagcctc  | acagctgtat  | tcatgtggcc  | tggaaggac   | agccgctggc  | 1200 |
| tgccaagctg  | gntgctggcc  | cggctggtgt  | ttgtgccact  | gctgctgctg  | tgcaacatta  | 1260 |
| agccccgccg  | ctacctgact  | gtggtcttcg  | agcacgatgc  | ctggttcac   | ttcttcatgg  | 1320 |
| ctgcctttgc  | cttctccaac  | ggctacctcg  | ccagcctctg  | catgtgcttc  | gggcccaga   | 1380 |
| aagtgaagcc  | agctgaggca  | gagaccgcag  | agccatcatg  | gccttcttcc  | tgtgtctggg  | 1440 |
| tctggcactg  | gggctgttt   | tctccttct   | gttcgggca   | attgtgtgac  | aaaggatgga  | 1500 |
| cagaaggact  | gcctgcctcc  | ctccctgtct  | gcctcctgcc  | ccttcttct   | gccaggggtg  | 1560 |
| atcctgagtg  | gtctggcggt  | ttttcttct   | aactgacttc  | tgctttccac  | ggcgtgtgct  | 1620 |
| gggcccggat  | ctccaggccc  | tggggaggga  | gcctctggac  | ggacagtggg  | gacattgtgg  | 1680 |
| gtttggggct  | cagagtgcag  | ggacgggggtg | tagcctcggc  | atttgcttga  | gtttctccac  | 1740 |
| tcttggtct   | gactgatccc  | tgctgtgca   | ggccagtggg  | ggctcttggg  | cttggaagac  | 1800 |
| acgtgtgtct  | ctgtgtatgt  | gtctgtgtgt  | ctgcgtccgt  | gtctgtcaga  | ctgtctgcct  | 1860 |
| gtcctggggg  | ggctaggagc  | tgggtctgac  | cgttgatagg  | tttgacctga  | tatactccat  | 1920 |
| tctccctgc   | gcctcctcct  | ctgtgttctc  | tccatgtccc  | cctcccaact  | ccccatgcc   | 1980 |
| agttcttacc  | catcatgcac  | cctgtacagt  | tgccacgtta  | ctgccttttt  | taaaaatata  | 2040 |
| tttgacagaa  | accaggtgcc  | ttcagaggct  | ctctgattta  | aataaacctt  | tcttgttttt  | 2100 |
| ttctccatgg  | aaaaaaaaa   | aaaaaaa     |             |             |             | 2127 |

&lt;210&gt; 158

&lt;211&gt; 1625

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1066)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 158

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| caaaagatct | ataatcagga | cattgtttat | gtaagttgga | caanaaaat  | tcttccccctt | 60  |
| tatgtccacc | cttccatga  | ttgcaagaca | aaatttccct | cctttacctc | atccctataa  | 120 |
| catgggaggc | tgagaaaaat | gaggggagat | ggaaccagat | acaaggagat | ccaataagag  | 180 |

|             |             |             |            |            |            |      |
|-------------|-------------|-------------|------------|------------|------------|------|
| aagcttattt  | aaatattgtg  | aaataaagga  | agamccaaag | cattttttta | agtggggaat | 240  |
| ccttttgaa   | agttattatt  | tatccatatt  | attaayaaca | tcttttctga | caaaatccat | 300  |
| cagatgaagt  | gtaaatggat  | aatcttttaa  | tggatctaaa | cctagaaagt | ttcacttact | 360  |
| gttcatgtcc  | gtgttccaga  | attgtgaaat  | gggtgtgtgt | tttgctttcc | aagttcttct | 420  |
| ctgcctcctc  | ttaattctct  | aattccatgt  | cttacagaag | aatgagaaat | ttctttctta | 480  |
| cttgagtatc  | atgctctaaa  | aaacttggct  | tcagtcacag | aaacgctggc | tctcctgtgc | 540  |
| ttatattgaa  | gccaaactgcc | tttaattctt  | gggccctctt | atatttttaa | ggtgcaaaat | 600  |
| ttgaagtctc  | agtcaccaga  | cacaggttct  | atacaattaa | tgatgagctg | gagaagtaat | 660  |
| atgtagctaa  | tttttcaaaa  | gcattgaata  | tactttccgg | aaagaaaaca | gaaattaaat | 720  |
| attgccacat  | cttgccagaa  | tcccatctga  | caccttaact | ttgtcagggt | tcctacaact | 780  |
| tgctaatacaa | gtttttatata | ttctaaatct  | ccccagtttc | tttggggctg | gaagatgcaa | 840  |
| cttccattta  | atagaaaactt | tgaaatcttg  | gggtaaggga | gcagtggggg | gactagggag | 900  |
| aaggataaga  | aatagaatta  | ttgaaaagcc  | cccaccaggg | accttcctgg | ccagaatatg | 960  |
| cagagtaatt  | cctgctggct  | tcacctttga  | aagtcctctg | aaactatgca | gatgaaactg | 1020 |
| agtctgtttt  | tgatattgtc  | agatgtattc  | taccttgga  | gtcccnacac | ctaaactgga | 1080 |
| attcttgtat  | ttacatctcc  | tccactgtcc  | cccacaccac | ccctcaattc | ctgctgcccc | 1140 |
| tgctaagtgt  | aagcattttt  | ctcttgttat  | catcagggtc | acattaaaam | cagrtactta | 1200 |
| caaactgact  | tgaagcacag  | atacttttac  | gaatgtgata | aaatattttc | ttaagaaaag | 1260 |
| gaaagaggat  | gtgggtcaaa  | taaaacaccg  | catggatgtt | gattggtgaa | tactgggtga | 1320 |
| agaaaaggga  | gctcaggaat  | ttttattact  | gtatttgtaa | atgagtttga | aggaatttgt | 1380 |
| aaatgccact  | ggtacatttt  | taagggtgaca | catttgctcc | ttataaagtt | attaaaaatt | 1440 |
| acagggtgaag | cttaaatgac  | gtttgccagt  | agttttactt | tatataatca | atattgatat | 1500 |
| tgttgtctgaa | ctatgtaact  | ttatgatgca  | tttttcagtc | ccttttcaga | gcaaagtctt | 1560 |
| ttgcaatggg  | agtaatgttt  | agtttaaatt  | gacttaataa | attmttacct | gagcaaaaaa | 1620 |
| aaaaa       |             |             |            |            |            | 1625 |

&lt;210&gt; 159

&lt;211&gt; 1687

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (334)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (505)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1044)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1670)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1678)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1683)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1684)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 159

|             |             |            |             |            |            |      |
|-------------|-------------|------------|-------------|------------|------------|------|
| cggggtcacc  | agttattaga  | ggaagtaaca | caaggggata  | tgagtgcagc | agacacattt | 60   |
| ctgtccgatc  | tgccaagggg  | tgatatctat | gtgtcagatg  | ttgaggacga | cggtgatgac | 120  |
| acatctctgg  | atagtgcact  | ggatccagag | gagctggcag  | gagtcagggg | acatcagggg | 180  |
| ctaagggacc  | aaaagcgtat  | gcgacttact | gaagtgcgaag | atgataaaga | ggaggaggag | 240  |
| gaggagaatc  | cactgctggt  | accactggag | gaaaaggcag  | tactgcagga | agaacaagcc | 300  |
| aacctgtggt  | tctcaaaggg  | cagctttgct | gggnatcgag  | gacgatgccg | atgaaggccc | 360  |
| tggagatcag  | tcaggcccag  | ctgttatctg | agaaccggyg  | gaagggacgg | cagcagcagc | 420  |
| agaagcagca  | gctgccacag  | acaccocctt | cctgtttgaa  | gactgagata | atgtctcccc | 480  |
| tgtaccaaga  | tgaagccocct | aaggnaacag | aggcttcttc  | ggggacagaa | gctgccactg | 540  |
| gccttgaagg  | ggaagaaaag  | gatggcatct | cagacagtga  | tagcagtact | agcaktgagg | 600  |
| aagaagagag  | ctgggaaccc  | tccgtggtaa | gaagcgaasc  | gtgggcctaa | agtcagatga | 660  |
| tgacgggttt  | gagatagtg   | ctattgagga | cccagcgaaa  | catcggatac | tggaccccca | 720  |
| aggccttgct  | ctaggtgctg  | ttattgcctc | ttccaaaaag  | gccaagagag | acctcataga | 780  |
| taactccttc  | aaccggtaca  | catttaata  | ggatgagggg  | gagcttccgg | agtggtttgt | 840  |
| gcaagaggaa  | aagcagcacc  | ggatacgaca | gttgctgtgt  | ggtaagaagg | aggtggagca | 900  |
| ttaccggaaa  | cgtggcggg   | aatcaatgc  | acgtcccatc  | aagaaggtgg | ctgaggctaa | 960  |
| ggctagaaag  | aaaaggagga  | tgctgaagag | gctggagcag  | accaggaaga | aggcagaagc | 1020 |
| cgtggtgaac  | acagtggaca  | tctncagaac | gagagaaagt  | ggcacagctg | cgaagtctct | 1080 |
| acaagaaggc  | tgggcttggc  | aaggagaaac | gccatgtcac  | ctacgttgta | gccaaaaaag | 1140 |
| gtgtggggccg | caaagtgcgc  | cggccagctg | gagtcagagg  | tcatttcaag | gtggtggact | 1200 |
| caaggatgaa  | gaaggaccaa  | agagcacagc | aacgtaagga  | acaaaagaaa | aaacacaaac | 1260 |
| ggaagtaagc  | agagctgcc   | ggctcccagg | agagcatggg  | gactaggagg | aagggtgtgg | 1320 |
| catggctcag  | tctggccccc  | ttgattaccg | gcctagcccc  | tgctcacatc | acagctgtct | 1380 |
| gaagaacagt  | gaggtggagt  | gcctagaact | cccgtgggtg  | tcctgagcag | agaggaggat | 1440 |
| gtcctcctgc  | ctgcctgaag  | gtctcccatg | aaaacactgc  | tgaactgtgt | tgacactcat | 1500 |
| gacccttttt  | ttaaaccgtt  | aaagggaagt | tcggtgttgg  | agcgatactc | aatgtagtca | 1560 |
| gtctacacct  | ggacgtgtgg  | gccacttaag | ccctccccac  | ccccatccta | ttcctraata | 1620 |
| aaaccaggat  | aatggaaraa  | aaaaaaaaaa | aaaaaaaaag  | ggggggcccn | taaagggncc | 1680 |
| cannttt     |             |            |             |            |            | 1687 |

&lt;210&gt; 160

&lt;211&gt; 1842

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (62)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1793)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1834)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 160

|             |             |             |             |            |            |      |
|-------------|-------------|-------------|-------------|------------|------------|------|
| ggatgacaga  | ttgcgacana  | gattttgtgac | ccttcctgct  | gaacttcaga | gggagctgaa | 60   |
| ancagcgtat  | gatcaaagac  | aaaggcaggg  | cgagaacagc  | actcaccagc | agtcagccag | 120  |
| cgcatctgtg  | ccccgagaat  | cctttacttc  | atctaaaggc  | agcagtgaag | gaaaagaaaa | 180  |
| gaaacaagaa  | gaaaaaaacc  | atttggttcac | caaaaaggat  | tcagagtcct | ttgaataaca | 240  |
| agctgcttaa  | cagtcctgca  | aaaactctgc  | caggggcctg  | tggcagtcct | cagaagttaa | 300  |
| ttgatgggtt  | tctaaaaacat | gaaggacctc  | ctgcagagaa  | acccctggaa | gaactctctg | 360  |
| cttctacttc  | agggtgtgcca | ggccttttcta | gtttgcagtc  | tgacccagct | ggctgtgtga | 420  |
| gacctccagc  | acccaatcta  | gctggagctg  | ttgaattcaa  | tgatgtgaag | accttgctca | 480  |
| gagaaatggat | aactacaatt  | tcagatccaa  | tggagaaga   | cattctccaa | gttgtgaaat | 540  |
| actgtactga  | tctaatagaa  | gaaaaagatt  | tggaaaaact  | ggatctagtt | ataaaataca | 600  |
| tgaaaaggct  | gatgcagcaa  | tcgggtggaat | cggtttggaa  | tatggcattt | gactttattc | 660  |
| ttgacaatgt  | ccaggtgggt  | ttacaacaaa  | cttatgggaag | cacattaata | gttacataaa | 720  |
| tattaccaga  | gagcctgatg  | ctctctgata  | gctgtgccat  | aagtgtctgt | gaggtatttg | 780  |
| caaagtgcac  | gatagtaatg  | ctcggagttt  | ttataatttt  | aaatttcttt | taaagcaagt | 840  |
| gttttgtaca  | tttcttttca  | aaaagtgcc   | aatttgtcag  | tattgcattg | aaataattgt | 900  |
| gttaattatt  | ttactgtagc  | atagattcta  | tttcaaaaat  | gtttgtttat | aaagttttat | 960  |
| ggattttttac | agtgaagtgt  | ttacagttgt  | ttaataaaga  | actgtatgta | tatttggtac | 1020 |
| rggctccttt  | tkgtgaaycc  | ttaaaaactc  | aactctagga  | rgcaactact | gtttattata | 1080 |
| ctaaarggct  | gaaaamcctc  | caggccagac  | tgctaagctc  | tgaaatycct | gagaggtctc | 1140 |
| agaccgggat  | tctacttggt  | ccaagaaagg  | gtaaagcttc  | taaaccatct | tattcttgct | 1200 |
| tccaagcatg  | aacacaggag  | catgtyaaga  | aaatctttac  | tactttctyc | catgctggga | 1260 |
| aatctacata  | ttttgaatta  | gaaacaccct  | cacacccact  | tgaagatttt | tttcctggga | 1320 |
| acattatgtc  | cgttagatca  | gaggtgggtg  | tgtctttttg  | cttctactgg | ccattgagaa | 1380 |
| actttgatga  | taaaaaagaa  | cggatatagat | ttttcaaacg  | tatatataat | atttttatgt | 1440 |
| tatatgttat  | gccataactt  | taaaataaaa  | atagtttaaa  | attctatgct | agtggatatt | 1500 |
| tggaaactttt | tcctcaaaaca | aacacccac   | actgacttca  | gcaaaaacct | aaaactagct | 1560 |
| acagattact  | actacgaatg  | aatcatyaag  | ttttgtgtct  | gcaacaattt | agaagcacta | 1620 |
| agcccaaata  | tcaggaaatg  | tgtgtatgat  | ggaattttct  | aggacaaaac | agatcaagat | 1680 |
| taaaacagga  | tcaaggatta  | atgggtataaa | aatgggtctac | taaaacagga | tcaaggatta | 1740 |
| aaacaggatc  | aaggattaat  | ggtataaaaa  | tcctactctg  | ttaccgggtg | gcngggccat | 1800 |
| acagggtagt  | ggtggatgga  | tagtttagtt  | tggnaagggt  | aa         |            | 1842 |

&lt;210&gt; 161

&lt;211&gt; 770

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (744)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 161

|            |             |            |            |            |             |     |
|------------|-------------|------------|------------|------------|-------------|-----|
| ggcacgagcc | ctatgctggt  | cttgtgataa | tgagtgagtc | tcacaagatc | tggtgggtgt  | 60  |
| ataggcatct | ggcatttccc  | ctgtgacgc  | tcattctcta | tcctgccacc | ctgggaagaa  | 120 |
| gtgtcttctg | tcattgattgt | aagtttctct | aggcctcccc | agctatgtag | aactgtgagc  | 180 |
| caattaaacc | tcttttctct  | ataaattatc | cagctctata | tatttcttca | tagcagtggtg | 240 |
| agaacagata | ataccgtaaa  | ttggtatcac | agagagtggg | gtgttgctat | aaacacatct  | 300 |

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| gaaaatgtta | aagcaaattt | ggaactgggt | aacaggcaaa | ggctggaaca | gttkgaagaa  | 360 |
| cagttaagaa | gaagacagga | aaatatgaga | aatcttgaaa | cttcctagag | tcttaaagggt | 420 |
| ctcagaagac | atgaagatgt | gggaagcttt | ggaacttcct | agagacttgt | ttgaatggct  | 480 |
| ttgacaaaa  | tgctgatagt | gatatggaca | atgaagtcca | ggctgagctt | atccagacag  | 540 |
| acataagaag | ctcgctggga | acttgagtaa | agatcactct | tgctaggcaa | agagactgggt | 600 |
| ggcctttttt | cctctgccct | agagatctgt | ggaaatctga | acctgagaga | gatgatttag  | 660 |
| ggtatctggc | agaagaaata | tctaagcggc | aaaaccttcm | agaggaagca | gagcataaac  | 720 |
| gtttgaaaaa | tttgcagcct | gacnatggga | gaccaaagtt | aaacccaatt |             | 770 |

<210> 162  
 <211> 519  
 <212> DNA  
 <213> Homo sapiens

|            |            |            |            |             |            |     |
|------------|------------|------------|------------|-------------|------------|-----|
| <400> 162  |            |            |            |             |            |     |
| gaattcggca | cgagctgaga | ggcacaggag | caacagccag | tgccccctgc  | agaggaccac | 60  |
| tggggtcaca | gacttcarac | ctgatgacct | gggctcagat | cccagctctg  | cacctaccag | 120 |
| ccgtgtgaca | aggtgtcctc | tctgagcctc | agtcacacac | tgcttaacg   | gttgggcctc | 180 |
| atggagctgt | ttgtgaaggt | taaatgggaa | gacataaagc | acttagccca  | gagccaagga | 240 |
| catgtgaat  | aggataatgg | tggcctcctt | tggcgctgtg | ctgggtgcagg | tgtgccgagg | 300 |
| aaytgggcag | gggtgacaga | tacctcttct | aacctagttc | ctttccaaga  | acctaattgg | 360 |
| tgtctctccc | tccccaggc  | aattggaagg | aggaggctgg | gccccagccc  | cagaatacgg | 420 |
| gaggtttctc | accgtggtag | ggaaattgct | gggttggggg | tgtgggcaac  | cacagtgatc | 480 |
| gtctctctgc | aggacggatg | aggctttgct | gacagaggc  |             |            | 519 |

<210> 163  
 <211> 753  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (720)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (730)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (736)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (741)  
 <223> n equals a,t,g, or c

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 163  |            |            |            |            |            |     |
| ggcacgagcg | gcacgagcag | ccagttgctg | actggcacat | ggcctccagc | gtccccgctg | 60  |
| gtgggcacac | tagagccgga | gggatcttct | taattggtaa | attggatctt | gaagcttcac | 120 |
| tgtttaaatc | ttttcagtg  | cttccctttg | tacttagaaa | aaaatgcaac | ttcttctgct | 180 |
| gggactcatc | cgtccacagc | cttccoctcc | accctctctc | tgctcatgc  | tctgccccgt | 240 |
| cctgcatgc  | ctccgatact | caccttttgt | accccagcac | ccgtgccctc | tgccccctga | 300 |

105

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| tctttgcctg | gctgggttgc | cctcactcag | tgttcaggac | aaatgctcct | ggccctaccc  | 360 |
| catctagcca | gtctagcccg | gtcttcctgt | tcttcctgt  | ttcattcatg | gctcttattg  | 420 |
| tttgttwact | tgtgtgctgt | tgacttttaa | ctctctcagt | ccccactgga | atgcaagcga  | 480 |
| tctcccaagc | tcctagaatt | gttcctgcct | cttcacagc  | ccttacgctg | tgtgtgctcg  | 540 |
| tgccgaattc | ggcacgaggg | tatgtgcact | tgctggtagt | tatgtagggt | tttgctaaca  | 600 |
| catacgtgca | cacgcagaat | gcttccaggg | gactgcacag | cctctagttc | gcagccccca  | 660 |
| cccctccctt | tgsccttgca | ctctccctc  | tctgagctgc | attcgcatga | aaggggtgcan | 720 |
| ggttcctgan | cccgcnagcg | ncacctcctg | gga        |            |             | 753 |

&lt;210&gt; 164

&lt;211&gt; 1893

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 164

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| tcgagttttt  | tttttttttt  | ttttttttkt  | aattttaaaca | aataccaaaa  | gctttatttta | 60   |
| agcaaaaaa   | cattcaacca  | cagaacattc  | agaaagctaa  | caggatcatt  | tctacattca  | 120  |
| ttctgcaaac  | agtgtagtaa  | gaaaggtaat  | ttgagaattt  | ccaaagatgt  | tctcgctagc  | 180  |
| cattatattat | ggttaattaca | taacattttg  | atgtcaagtt  | attacagact  | taaaagttaa  | 240  |
| tatagcataa  | ttttacaatc  | gtactttcac  | tatgattttt  | attttaaccc  | tggatattat  | 300  |
| tggtttgaag  | ctaataattat | cagtcctatt  | ggctgtcact  | gtcacagatc  | tgaagatatg  | 360  |
| tttaaattca  | tcaagctagg  | aagatatcaa  | aatattaaca  | atcttcaagt  | atagtgagaa  | 420  |
| aaaaactgat  | ttaagtgtta  | gcattttctaa | acttgagact  | ctaacagtaa  | aaacaaagta  | 480  |
| atctgaaacc  | tgtttccatg  | ggtaaaacac  | tctgcctggg  | attcttgtac  | acaaaattta  | 540  |
| ctaaatatgt  | gaatatcata  | aaatgaaaat  | atcactccct  | tcaatttctt  | tggccttcac  | 600  |
| aaattcaatg  | tgactatgat  | ccttttcaat  | aatacttyca  | atgacattgt  | gcttcttttag | 660  |
| aaaaatcact  | taagtgttag  | catacaatag  | ttaacattag  | ttcttttatt  | gctatgggtat | 720  |
| atgctaattt  | ttttaaaagg  | ggaaaaaaaa  | acccagagaa  | cttattaaaa  | tgtttggttaa | 780  |
| agcaaacatt  | tcagttgggt  | tccttttctt  | gaagaataat  | agaaataaat  | gtcagaggag  | 840  |
| tattactaag  | gagccaaaac  | aaacaaacaa  | acaaaaaaac  | aaaaaactcc  | tttattactc  | 900  |
| ccatcctcag  | aactaactca  | agacaagaga  | tctgtattca  | aaaagataaa  | acaatctcat  | 960  |
| ctcagtaact  | acctcctatg  | aaacctaaga  | gagaaaacct  | gtaatagctc  | tcttaaccaa  | 1020 |
| cagccccatc  | tgacatcac   | caagcaccag  | ttccctttgg  | gtagcagtaa  | tgcttgtttt  | 1080 |
| tcatctttgc  | atattagga   | ctggtgttaa  | cagatttatg  | ggtcatttgt  | agcttaacttt | 1140 |
| gcaataacct  | ttcacttctt  | atgaaacaca  | atatgcccc   | aaacatggac  | cattattcaa  | 1200 |
| gtagacaaaa  | tcactcactg  | acagcacttt  | aacaaccgc   | ctccactyca  | tcttcccatt  | 1260 |
| ctctcaccct  | atgccttcca  | atgaacctag  | tctttgctag  | tgatgagtc   | atctggggac  | 1320 |
| aaatactgct  | ttaaagatga  | tgtaattttc  | aatgcccaacc | acagtgactt  | tcccataata  | 1380 |
| ggtattaata  | aacacttggt  | gacatagtta  | taataagcta  | aaaatagtta  | acattaattt  | 1440 |
| tgctctttat  | cttttattct  | tatggcatag  | aattttattt  | aaaagactga  | aaaactgatt  | 1500 |
| ccaatgtaat  | aatcacttac  | tgggccacac  | gctagatgac  | agacatgcct  | ccctgcctaa  | 1560 |
| aaagggctca  | aaggaaactc  | cagttataca  | tgagtgaatt  | aaaactttta  | atgtactaca  | 1620 |
| agaaagaact  | ttttatatga  | aggattcttt  | atgtagagta  | tcttttttga  | aaaatcagat  | 1680 |
| tttcttatcc  | tatattacac  | tggttttaat  | tgggcatgct  | cacttttagtg | gtgtgcctca  | 1740 |
| ttacaatgtc  | tcttttgtgt  | taagaattaa  | cttacaaaag  | catttaaaaa  | tcactacatc  | 1800 |
| aaatgggata  | gagagtaaga  | agacaggaga  | gagaggagaa  | accatgtttt  | ttcggacgcg  | 1860 |
| tgggtcgacc  | cacgcgtccg  | cggacgcgtg  | ggc         |             |             | 1893 |

&lt;210&gt; 165

&lt;211&gt; 2153

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (101)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1670)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2134)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2135)

<223> n equals a,t,g, or c

<400> 165

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| caggcctcag  | ggcctctggg | ggcctctggc  | cagacagtat  | ttgcagttct  | tgtgctatgg  | 60   |
| gtgggagctc  | tcttcctcaa | gtttcggcag  | ctgtgctgtg  | notggatggg  | ctgctcctcc  | 120  |
| cagggctcaa  | gggctgtggg | ccgctcaggg  | tctcatttcc  | ccaggccaag  | ttcaaggcag  | 180  |
| cagccctttg  | tgaggcgctc | ttggccctgg  | gctggaggga  | gaactttaag  | cttttttgc   | 240  |
| cacagggacg  | tggatggggc | cctgggtgca  | gggtgcccaca | ttctgcta    | gagagctttg  | 300  |
| tctgatcagt  | cctgggtcca | tcagtgtgtc  | catgtgtccg  | gctgccagcc  | cgtcccttgg  | 360  |
| gacccctccc  | ctggggtgta | gccttgttca  | ttagtata    | ctcattcctt  | catgctttcc  | 420  |
| tcagcagaac  | acttccactt | ctgaggtgag  | cttttgcccc  | rtgcccttcc  | tcacaggtg   | 480  |
| ttgccttttt  | ataaagacct | gatagcagaa  | taaattgggtg | tttccctgtt  | gacccagcac  | 540  |
| catttctgtg  | ggcctagaat | atggccctca  | acccttagag  | tggggcagtg  | agggcctgag  | 600  |
| gagtgcacct  | tcctttctca | tgggttttagt | cattttggct  | gccagccctt  | aatggcacag  | 660  |
| atctgctgct  | tctaacagat | ggccaggagg  | tgacaccgat  | ttcagccatt  | gccaagggtta | 720  |
| gcacccctctc | ctttgagcct | agggccacac  | tggtcattgt  | cacttttaggc | aagtgcctgt  | 780  |
| ttggctttta  | aggtaaacct | gccagctgtg  | agaagccttg  | gtaactgatg  | gactcatttc  | 840  |
| ctggctcctta | aagatgcagc | ctcttaaggg  | ctccttgatg  | gatgccatct  | ctcctagccc  | 900  |
| ccagccctgg  | tgccactggg | gggcaggttc  | ccattctttg  | gggctgggag  | ggacagcttg  | 960  |
| cctgtttctg  | gtcacaatt  | acagtcttct  | ctcctgtacc  | attctgtggc  | ttcagcatgg  | 1020 |
| gggcagtagc  | ctttcattag | tgtagatagt  | cattccctgg  | taggggtggag | ggtaagacat  | 1080 |
| agggctctgga | actgtttggg | accttttggg  | gatgtcctgt  | gcctcccaga  | ttcctmgatt  | 1140 |
| ctgggaggag  | aggtgcccgc | attctgctgc  | tcctcacagc  | gagcaaagct  | gcacccactt  | 1200 |
| acattcagta  | ttttcctggc | actacaaaga  | gtgggaaggc  | ctgggatttg  | ctgctgctcc  | 1260 |
| cttagagcag  | ggcccttytt | ttcagcactt  | tggacacctg  | gagaccagc   | cctgttattt  | 1320 |
| aatggtagtg  | ggcaagtgtg | tgtgcatact  | gtctgccact  | gctttctccc  | tgcccatgc   | 1380 |
| cagagagccc  | tgtccctgcc | aggcccagcc  | ttcttagccc  | caacttggga  | acaaagtga   | 1440 |
| acatgggatc  | atgggttggg | gtgctcaggt  | gagccctctc  | tatagtgtt   | ccctgggcca  | 1500 |
| agctgacacc  | agcccttgag | gggtgggtgg  | gacgggtggg  | gcttaaaaga  | ggaaggggac  | 1560 |
| cagtgtagca  | acttgccagg | gacccacccc  | ctccctctct  | gggcctgtgc  | agtgagcatg  | 1620 |
| gggattccca  | tcaagggggc | tggcacctgt  | gctagttagc  | tagccgctgn  | tcacgcgctc  | 1680 |
| actcctgacc  | acatgcacgt | tccctagatg  | cagactgctt  | tgaacttta   | agctgtacaa  | 1740 |
| tttggttatg  | tttgtgctga | cttaaaatat  | attttaatga  | ggaaaaata   | atggagaacc  | 1800 |
| ctgggaaggc  | cctggttctt | ttgcttctcg  | gggaactgta  | agccctcgcg  | ttctgggaat  | 1860 |
| cgctctctgc  | tgtcttttcc | tggaaagctaa | gcctgtctcc  | accgcccagag | gcctgcgcgcg | 1920 |
| gtgctcccgc  | cgcagttgcg | tttgccttgg  | accttgctgtg | cgggggaggg  | ggtgctcggt  | 1980 |
| ccgagcccgc  | tcctttctgt | acacctagcg  | ctgcccgcgc  | cgcttgtgtc  | tgaggtcggtg | 2040 |
| tatgtcaaaa  | ataaagccgc | tagaaacgga  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | 2100 |
| aaactcgagg  | gggggcccgt | acccaattaa  | cccnntatga  | tctataaagc  | gtc         | 2153 |

<210> 166

<211> 1251



&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 166

|            |            |            |            |            |             |      |
|------------|------------|------------|------------|------------|-------------|------|
| gccacgcgt  | ccgccacgc  | gtccggcggt | gcggagtatg | gggcgctgat | ggccatggag  | 60   |
| ggctactggc | gcttcctggc | gctgctgggg | tcggcactgc | tcgtcggctt | cctgtcgggtg | 120  |
| atcttcgccc | tcgtctgggt | cctccactac | cgagaggggc | ttggctggga | tgggagcgca  | 180  |
| ctagagttta | actggcacc  | agtgtcatg  | gtcaccggct | tcgtcttcat | ccagggcatc  | 240  |
| gccatcatcg | tctacagact | gccgtggacc | tggaaatgca | gcaagctcct | gatgaaatcc  | 300  |
| atccatgcag | ggttaaatgc | agttgctgcc | attcttgcaa | ttatctctgt | ggtggccgtg  | 360  |
| tttgagaacc | acaatgttaa | caatatagcc | aatatgtaca | gtctgcacag | ctgggttgga  | 420  |
| ctgatatctg | tcatatgcta | tttgttacag | cttctttcag | gtttttcagt | ctttctgctt  | 480  |
| ccatgggctc | cgttttctct | ccgagcattt | ctcatgcca  | tacatgttta | ttctggaatt  | 540  |
| gtcatctttg | gaacagtgat | tgcaacagca | cttatgggat | tgacagagaa | actgattttt  | 600  |
| tccttgagag | atcctgcata | cagtacattc | ccgccagaag | gtgttttcgt | aaatacgctt  | 660  |
| ggccttctga | tcctgggtgt | cggggccctc | attttttgga | tagtcaccag | accgcaatgg  | 720  |
| aaacgtccta | aggagccaaa | ttctaccatt | cttcatccaa | atggaggcac | tgaacaggga  | 780  |
| gcaagagggt | ccatgccagc | ctactctggc | aacaacatgg | acaaatcaga | ttcagagtta  | 840  |
| aacagtgaag | tagcagcaag | gaaaagaaac | ttagctctgg | atgaggctgg | gcagagatct  | 900  |
| accatgtaaa | atgttgtaga | gatagagcca | tataacgtca | cgtttcaaaa | ctagctctac  | 960  |
| agttttgctt | ctcctattag | ccatatgata | attgggctat | gtagtatcaa | tattttacttt | 1020 |
| aatcacaaag | gatggtttct | tgaaataatt | tgtattgatt | gaggcctatg | aactgacctg  | 1080 |
| aattggaaag | gatgtgatta | atataaataa | tagcagatat | aaattgtggg | tatgttacct  | 1140 |
| ttatcttggt | gaggaccaca | acattagcac | ggtgccttgt | gcakaataga | tactcaatat  | 1200 |
| gtgaatatgt | gtctactagt | agttaattgg | ataaactggc | agcatccctg | a           | 1251 |

&lt;210&gt; 167

&lt;211&gt; 882

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (522)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (752)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 167

|             |             |            |            |            |             |     |
|-------------|-------------|------------|------------|------------|-------------|-----|
| gacsmcttag  | aactatggtc  | ccccgggact | gcaggaattc | ggcacagcgg | ctgcggggcgc | 60  |
| gaggtgaggg  | gcgcgagggt  | cccagcagga | tgccccggct | ctgcaggaag | ctgaagttag  | 120 |
| aggcccggag  | agggcccagc  | ccgcccgggg | caggatgacc | aaggcccggc | tgttccggct  | 180 |
| gtggctgggtg | ctggggctcg  | tgttcatgat | cctgctgata | atcgtgtact | gggacagcgc  | 240 |
| aggcgccgcg  | cacttctact  | tgcacacgtc | cttctctagg | ccgcacacgg | ggccgcccgt  | 300 |
| gcccacgccc  | gggcccggaca | gggacaggga | gtcacgggcc | gaytccgatg | tcgacgaktt  | 360 |
| tctggacaak  | tttctcagtg  | ctggcgtgaa | gcagagtgc  | yttcccagaa | aggagacgga  | 420 |
| gcagccgcct  | gcgcccggga  | gcatggagga | gagcgtgaga | rgctacgact | ggtccccgcg  | 480 |
| cgamgcccgg  | cgaccccaga  | ccagggccgg | cagcargcgg | ancggaggag | cgtgctgcgg  | 540 |
| ggcttctgcg  | ccaaytccag  | cctggccttc | cccaaccaag | agcgcgcatt | cracgacatc  | 600 |
| cccaactcgg  | agctgagcca  | cctgatcgtg | gacgaccggc | acggggccat | ctactgctac  | 660 |
| gtgcccaggg  | tggcctgcac  | caactggaag | cgcgtratga | tcgtgctgag | cggaagctgt  | 720 |
| gcaccgcgtg  | cgcctaccgc  | gaccggytgc | gntcccgcgc | gagcacgtgc | acaacgccag  | 780 |
| cgcgcactga  | cttcaacaat  | tctggcgccg | ctacgggaag | tctccccac  | ctcatgaagt  | 840 |
| caagctcaag  | aatacaccaa  | ttctttctgc | gcgacccttc | tg         |             | 882 |

<210> 168  
 <211> 1208  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (161)  
 <223> n equals a,t,g, or c

<400> 168  
 ttccaggaggaa aaataagttc tgtatatgtt ttagctaaat agtattattt ttgtcatatt 60  
 cccaaattgg aagtcccagt acatatttag ctattacaat tctaagttat ttgcagtaaa 120  
 gaatatagat gaagctggtc tcatttctat tttccaagtk nytggggggcc atagtgattt 180  
 ttttttaacc tgacaacacc tcagggaat ttatggttta cagagcacia cattgtaaat 240  
 tatggcagaag taaaaaagaa aacactgaat ttcaacttgg aaaatcagaa tgctgttgct 300  
 aatagtatta gtagcaaata tattaagtat gtcaaatatg tcaaatgctg ttgtaagtga 360  
 ttacatata ttagtacatt taatctcaca taaagcaaat taagtaatat cattagctcc 420  
 attctacaga tataaagacc gagactcagg traattaagg tactcaccca aatttacata 480  
 gcagaactga aattcaaact tatgcaatta gtctccagtc taagatttta actgcactgt 540  
 tattctgtcg ctgttaccta ctaattgggt wacctgtggc aagctatttt accyctctaa 600  
 gtcaagctgt ttattgatca gacagattaa kgttwtctga wgtggsgkgtc mtaaggratc 660  
 agtattttaac agagtcaaat gcagtgcctg aaatatgcag ttggtactca taatamttat 720  
 ttattaaatg agaytcaaga actctagatt tgggtatcyt cctagctgtg wamacacagc 780  
 tatttgttac ctatcggtat tagaggaaca ggcataaagc tgtgctgagy tgcttgacgg 840  
 aaaattccca ctctagaact tcaactggat ctttagaact aatcattaat cttggattta 900  
 cccaggttga ttgcccattg caactcatat cacaggcatt tcacgtactg tatgcattcc 960  
 tcaaacagg gcagggggat caggaaatga tttaaacccg tcaactgagg agccccagga 1020  
 ggaccatgca ctggctgccc tgacatttta ccaaatgtgg ctgtcctgtc atgatctttt 1080  
 cttaagaatc cctacgtaat tccaaagcta atattwaaat atacgtaaat acctctatct 1140  
 tcaactctga tcccttyact tctaggctct ggctccatca accattccat catccttttg 1200  
 agtttccc 1208

<210> 169  
 <211> 1258  
 <212> DNA  
 <213> Homo sapiens

<400> 169  
 ggcacgagag aaaagaggtt gagaatgttt tctagcaggc agaatgtgca tacatgtttt 60  
 catgagtgtc ctttgggtgc tgtttctttt aaatcctctg tgcacagggc tctggccttt 120  
 agtaaaactgt ttttctgtct tacgtcatgc tgactgggtg ctaggggctg attacaaagg 180  
 ggaagagttg aacagacatc aggggccgat gaaaccaaag gactaggagt caggagaaca 240  
 agtcagggat taggagacag cggtttggtt tattgttatc cagctggagg actcctaggg 300  
 gcagcagcag gaggaatacc agggccacgg agggccacag agtctcacag tggagggcag 360  
 actctaacag atgccagctg aacgctcgct ggccctggat gtcatacgag ttggggacca 420  
 gaaatctggg ctacagagaac ccgtccaggg agatttgaag ccatgggtta tcttctagag 480  
 ttgatactga taatatattt taatttttat tgatgtttta taccttctga aacaggaggg 540  
 taagatcaga tgggaagccc ctctgttgaa ggatcttggg aacttgggtg tttttttttt 600  
 ttggtttttt tttttttgat cgagctgtgg acatccttct taattcgatt ctgaggattt 660  
 gtttaactaa aaagttccca aacacagaaa gggcctcccc acctgctttg gggagctgtc 720  
 tgtgctggga gtgccaggca tccatggga cccatcactg ccagtgtctg tgcctcccag 780  
 aggtcagccc tgtgtctgcc ctggctctgt ctccctctgt acagggcaga gcatttctgg 840  
 tcagtttctc catggtgcct cccacccttt gtaaagtggg tggacatgat ggaattcagt 900  
 tgtctcacc tcatagcctg ggtgttgata ttcactttac ccgcaactcag acacaggcga 960

|            |             |            |            |            |            |      |
|------------|-------------|------------|------------|------------|------------|------|
| ccttgaagca | gttctcgggtg | tgtagagtc  | acgtgacagt | ccccacagcc | tccccagata | 1020 |
| gctgtgtgcc | tgtgcgctac  | tgctgtgcca | ttttcccaac | ttggcgtttc | actaaatgca | 1080 |
| gctgatctct | ctctctgtgc  | actcgtgac  | catgttgaac | aatacatgta | ggttcttttt | 1140 |
| ccacgcaatg | taagaacatg  | atatactgta | cgttggaag  | catttacctt | atttatatac | 1200 |
| ctgaatgttc | ctactacaca  | aataaacata | tattaaattc | taaaaaaaaa | aaaaaaaaa  | 1258 |

&lt;210&gt; 170

&lt;211&gt; 1624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 170

|             |            |             |            |             |             |      |
|-------------|------------|-------------|------------|-------------|-------------|------|
| ggcacgaggt  | gcgcgcgcgc | gccgcctgga  | attgtgggag | ttgtgtctgc  | cactcggtg   | 60   |
| ccggaggcga  | aggtccctga | ctatggctcc  | ccagagcctg | ccttcaccta  | ggatggctcc  | 120  |
| tctgggcatg  | ctgcttgggc | tgctgatggc  | cgcctgcttc | accttctgcc  | tcagtcacata | 180  |
| gaacctgaag  | gagtttgccc | tgaccaaccc  | agagaagagc | agcaccaaag  | aaacrgagag  | 240  |
| aaaagaaacc  | aaagccgagg | aggagctgga  | tgccgaagtc | ctggagggtg  | tccacccgac  | 300  |
| gcctgagtgg  | caggcccttc | agccagggca  | ggctgtccct | gcaggatccc  | acgtacggct  | 360  |
| gaatcttcag  | actggggaaa | gagaggcaaa  | actccaatat | gaggacaagt  | tccgaaataa  | 420  |
| tttgaaggc   | aaaaggctgg | atatcaacac  | caacacctac | acatctcagg  | atctcaagag  | 480  |
| tgacttgga   | aaattcaagg | agggggcaga  | gatggagagt | tcaaaggaag  | acaaggcaag  | 540  |
| gcaggctgag  | gtaaagcggc | tcttcgcgcc  | cattgaggaa | ctgaagaaag  | actttgatga  | 600  |
| gctgaatgtt  | gtcattgaga | ctgacatgca  | gatcatggta | cggctgatca  | acaagttcaa  | 660  |
| tagttccagc  | tccagtttgg | aagagaagat  | tgctgcgctc | tttgatcttg  | aatattatgt  | 720  |
| ccatcagatg  | gacaatgcgc | aggacctgct  | ttcctttggt | ggtcttcaag  | tggtgatcaa  | 780  |
| tgggctgaac  | agcacagagc | ccctcgtgaa  | ggagtatgct | gcgtttgtgc  | tgggcgctgc  | 840  |
| cttttccagc  | aaccccaagg | tccagggtgga | ggccatcgaa | gggggagccc  | tgcaagaagct | 900  |
| gctggtcatc  | ctggccacgg | agcagccgct  | cactgcaaag | aagaagggtcc | tgtttgact   | 960  |
| gtgctccctg  | ctgcgccact | tcccctatgc  | ccagcggcag | ttcctgaagc  | tcggggggct  | 1020 |
| gcaggctcctg | aggaccttg  | tgaggagaa   | gggcacggag | gtgctcgccg  | tgcgctgggt  | 1080 |
| cacactgctc  | tacgacctgg | tcacggagaa  | gatgttcgcc | gaggaggagg  | ctgagctgac  | 1140 |
| ccaggagatg  | tccccagaga | agctgcagca  | gtatcgccag | gtacacctcc  | tgccaggcct  | 1200 |
| gtgggaacag  | ggctgggtgc | agatcacggc  | ccacctcctg | gcgctgcccg  | agcatgatgc  | 1260 |
| ccgtgagaag  | gtgctgcaga | cactgggctg  | cctcctgacc | acctgcccgg  | accgctaccg  | 1320 |
| tcaggacccc  | cagctcggca | ggacactggc  | cagcctgcag | gctgagtacc  | aggtgctggc  | 1380 |
| cagcctggag  | ctgcaggatg | gtgaggacga  | gggctacttc | caggagctgc  | tggtgctctgt | 1440 |
| caacagcttg  | ctgaaggagc | tgagatgagg  | ccccacacca | ggactggact  | gggatgccgc  | 1500 |
| tagtgaggct  | gaggggtgcc | agcgtgggtg  | ggcttctcag | gcaggaggac  | atcttgccag  | 1560 |
| tgctggcttg  | gccattaaat | ggaaacctga  | aggccaaaaa | aaaaaaaaaa  | aaaaaaaaaa  | 1620 |
| aaaa        |            |             |            |             |             | 1624 |

&lt;210&gt; 171

&lt;211&gt; 2003

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1961)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1999)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 171

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ggcacgagcc  | agcttgacag  | aggaatcggg  | gaggtcctgt  | cctgaggctg  | ctgtccgggg  | 60   |
| ccggtggctg  | ccctcaaggt  | cccttcccta  | gctgctgagg  | ttgccattgc  | ttcttgccctg | 120  |
| ttctggcatc  | aggcacctgg  | attgagttgc  | acagctttgc  | tttatccggg  | cttgtgtgca  | 180  |
| gggcccggct  | gggctcccca  | tctgcacatc  | ctgaggacag  | aaaaagctgg  | gtcttgctgt  | 240  |
| gccctcccag  | gcttagtggt  | ccctccctca  | aagactgaca  | gccatcggtc  | tgacacgggc  | 300  |
| tttctgcatg  | tgacgccagc  | taagcatagt  | aagaagtcca  | gcctaggaag  | ggaaggattt  | 360  |
| tggaggtagg  | tggctttggg  | gacacactca  | cttctttctc  | agcctccagg  | acactatggc  | 420  |
| ctgttttaag  | agacatctta  | tttttctaaa  | gggtgaattct | cagatgatag  | gtgaacctga  | 480  |
| gttgacagata | taccaacttc  | tgcttggtatt | tcttaaatga  | caaagattac  | ctagctaaga  | 540  |
| aacttcctag  | ggaactaggg  | aacctatgtg  | ttccctcagt  | gtggtttcct  | gaagccagtg  | 600  |
| atatgggggt  | taggataggg  | agaactttct  | cggtaagtgt  | aaggagaate  | tcttgtttcc  | 660  |
| tcccacctgt  | gttgtaaaaga | taaaactgacg | atatacaggc  | acattatgta  | aacatacaca  | 720  |
| cgcaatgaaa  | ccgaagcttg  | gcggcctggg  | cgtggtcctg  | caaaatgctt  | ccaaagccac  | 780  |
| cttagcctgt  | tctattcagc  | ggcaacccca  | aagcacctgt  | taagactcct  | gacccccaa   | 840  |
| tggcatgcag  | cccccatgcc  | caccgggacc  | tggtcagcac  | agatcttgat  | gacttccctt  | 900  |
| tctagggcag  | actgggaggg  | tatccaggaa  | tggccctctg  | ccccacgggc  | gttttcatgc  | 960  |
| tgtaacagta  | cctaaagttg  | gtaagatgtc  | ataatggacc  | agtcctatgt  | atttcagtat  | 1020 |
| atacaactcc  | accagacccc  | tccaacccat  | ataacacccc  | acccctgttc  | gcttcctgta  | 1080 |
| tgggtgatac  | atatgtaaca  | tttactcctg  | ttcttgctga  | ttgttttttt  | aatgttttgg  | 1140 |
| tttgtttttg  | acatcagctg  | taatcattcc  | tgtgctgtgt  | tttttattac  | ccttggtagg  | 1200 |
| tattagactt  | gcactttttt  | aaaaaaaagg  | ttctgcatcg  | tggaaagcatt | tgaccagag   | 1260 |
| tggaaagcgt  | ggcctatgca  | gggtggattcc | ttcagggtctt | tcctttgggt  | ctttgagcat  | 1320 |
| ctttgctttc  | attcgtctcc  | cgtctttggg  | tctccagttc  | aaattattgc  | aaagtaaagg  | 1380 |
| atctttgagt  | aggttcgggc  | tgaaggtgtg  | ggcctttata  | tttgatccac  | acacgttggt  | 1440 |
| cttttaaccg  | tgctgagcag  | aaaacaaaac  | aggttaagaa  | gagccgggtg  | gcagctgaca  | 1500 |
| gaggaagccg  | ctcaaatacc  | ttcacataaa  | atagtggcaa  | tatatatata  | gtttaagaag  | 1560 |
| gctctccatt  | tggcatcggt  | taatttatat  | gttatgttct  | aagcacagct  | ctcttctcct  | 1620 |
| attttcatcc  | tgcaagcaac  | tcaaaatatt  | taaaataaag  | tttacattgt  | agttattttc  | 1680 |
| aaatctttgc  | ttgataagta  | ttaagaaata  | ttggacttgc  | tgccgtaatt  | ttaaagctctg | 1740 |
| ttgattttgt  | ttccgttttg  | atttttgggg  | gaggggagca  | ctgtgtttat  | gctggaatat  | 1800 |
| gaagtctgag  | accttccggg  | gctgggaaca  | cacaagagtt  | gttgaaagtt  | gacaagcaga  | 1860 |
| ctgcgcattg  | ctctgatgct  | ttgtatcatt  | cttgagcaat  | cgctcgggtc  | gtggacaata  | 1920 |
| aacagtatta  | tcaaaagagaa | aaaaaaaaaa  | aaaaaactcg  | nggggggggc  | cggtaaccaa  | 1980 |
| ttcgccttat  | agtgaaccna  | ttc         |             |             |             | 2003 |

&lt;210&gt; 172

&lt;211&gt; 786

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 172

|            |            |             |            |            |            |     |
|------------|------------|-------------|------------|------------|------------|-----|
| ggcacagcgg | cacgagaaga | ctttgggtgtt | taagagatta | atgtgttagc | cagaacaact | 60  |
| catttctcta | ccmgtgtgta | gtccattttat | ctttaaagat | tttctattgg | aataattttg | 120 |
| aaattacttt | cttagttttc | ttcattaaaa  | actaagaaaa | tgctttgttt | attatgaatt | 180 |
| gctattttct | ttgattatta | ttcttgagga  | aagtctatca | gacgtaattc | ttctgatttg | 240 |
| cttctaggct | agaggaaaat | gtgaaagatg  | acaaatgaaa | atttcaaagg | ttgtcagtag | 300 |
| tatgacttct | tttatcggtt | gtcattatca  | caaataatc  | aacataggac | ttttaaaaga | 360 |
| tattttgtac | atattggggc | ttagtaggat  | tttgcatgaa | tttttttttt | cttttatgcc | 420 |
| cagagagaaa | gagcaaagaa | ataaccaagg  | gtgatgtact | cgtattgaag | gtttaccaa  | 480 |
| taaggactgc | ttttattatg | aactatagtc  | tatatcttaa | gtaaatcaat | ttttctatta | 540 |
| tgtgtttttt | gttccctgcg | gcaagatctc  | tgaactttat | gcagagggtt | cttttaaaaa | 600 |
| aacaaagttg | aattttttta | tttcttgtaa  | tatttttttt | cattgatttc | tccaagtag  | 660 |
| agcagattca | aatctccttt | gtaccctatg  | tcttttttgt | tttgctatta | gctcagtag  | 720 |
| ccgtttctac | attttccttt | cctagaacca  | gtcaataaat | gacaaaaaaa | aaaaaaaaaa | 780 |
| actcga     |            |             |            |            |            | 786 |

<210> 173  
 <211> 1758  
 <212> DNA  
 <213> Homo sapiens

<400> 173  
 gggacgagcc ctgcccacct cctgcagcct cctgcgcccc gccgagctgg cggatggagc 60  
 tgcgcacggg gagegtgggc agccaggcgg tggcgcgagg gatggatggg gacagccgag 120  
 atggcggcgg cggcaaggac gccaccgggt cggaggacta cgagaacctg ccgactagcg 180  
 cctccgtgtc caccacatg acagcaggag cgatggccgg gatcctggag cactcgggtca 240  
 tgtacccggg ggactcgggt aagacacgaa tgcagagttt gagtccagat cccaaagccc 300  
 agtacacaag tatctacgga gccctcaaga aaatcatgcg gaccgaagct tctggaggcc 360  
 cttgcgaggc gtcaacgtca tgatcatggg tgcagggccc gcccatgcca tgtattttgc 420  
 ctgctatgaa aacatgaaaa ggacttttaa tgacgttttc caccaccaag gaaacagcca 480  
 cctagccaac ggtattttga aagcgtttgt ctggagttag aaagttctct tcttcaacac 540  
 gtcctcccc aggggtgtcc tccctgtgac ccagccgcct cgacttcggc ccgcttgctc 600  
 acgaataaag aactcagagt tgtgtgtgca atgcacaccc agacacacgc acgcacacac 660  
 acgcgcgcgc acacacatgc ttttttctgt tccctccgc tttctgaagc ctggggagaa 720  
 atcagtgaac gaggtgtttt gggtttattg ttatgtgggt tttcttttgt attttttttg 780  
 tttgttttgt ttttaaacat tcaaaagcaa ttaatgatca gacataggag aaacctgaa 840  
 tagaaacaaa acttttgaat gctggattca aaaaaaaaaa aaagttatct ggacagcttc 900  
 tttgagacta tttaaaaact ggtacaacag gtctctacaa cgccaagatc taactaagct 960  
 ttaaaagggtc aagaagtttt atggctgaca aaggactcgc gcaacgcaga aggcctttcc 1020  
 caccttaagc ttccggggat ctgggaattt taccoccatc ctctctgtt tgtctgagtc 1080  
 tcctctctct gcaagcaagg gctgaaatca ttttgtttgg ttgttttgag ggagagaggc 1140  
 ggggtggggg ggtgcaaatc tgccagcagc tcttacgtaa ggcatgtttt attggggagg 1200  
 gctgagcttt tattttctcc tctccagtgg gggtggcttt tattgtttct tgtttgggtt 1260  
 tggaatggaa atatggatag cagcataaag tacttttatt ttgacaaaat tcattttttt 1320  
 caacaatgga gacatagatt tgaccacaa taacttctcc cctctctttt ttactctgct 1380  
 caaaaagcat ctctcctccc attaccaac cttggctcata agtgtgcctg gctggtttgc 1440  
 agatatttgt tctgctttgt aaaaattggc cattagtgc tttattgaga tgatctctaa 1500  
 agagctatgc cctgacctac ccctgattct atgacattgg ggcccttctt ttgctgaaac 1560  
 tgccttacgt aatggtttta ctcttgaaa gagatttgac ggaatccatt ttatgccaaag 1620  
 tgtgcccctg cactgtttct gcaatatgtg gtgtatgctg tggatgctt gctgggaatg 1680  
 attataagtg tgtgtgtgtg gggggagtggt gtattacatg cattgctgaa gagtcaaaaa 1740  
 aaaaaaaaaa aaactcga 1758

<210> 174  
 <211> 1369  
 <212> DNA  
 <213> Homo sapiens

<400> 174  
 ggagccttgg tgggaattctg catcatcatc tccttttttt tttttttttt tttttttttt 60  
 tttttctct gggattatat cagaatacaa ctgaatgagc gattgggttg atccccgata 120  
 actgtgtcca tgggttatag tagaatcttg gccacatggg agactgctat tagctactgg 180  
 aggtgctgct ggtaaagcag gtgtaaaaga aggcctcact ggggactgct ggaagctggt 240  
 cccagaaaga tttccatgtc cctgcttcac agaagaaaaa tttgggcttc caacagggat 300  
 tgatggtgaa tcaggaacaa atgaaggagg gcctacctgc cttcgctcat tagctgcat 360  
 gaaagtgttg gtggagggtg aattaattga tccttggtgt atattctgct gctgtgaaac 420  
 ctgccccatt tgctgttggt gttgtggaga ctgctgaagg ggtcctagag gttgcataaa 480  
 atcacaaggt aagtcggaac tgtagaaggg aatctgggac acagatgtcc tactactact 540  
 tatctcagag cccaccatac catgctgtct catttccatc ctctgtgca aagctctttg 600  
 tctatctacc tcctgcatga gttggatccg ttgtctctct tgctgttctc gtaaacgttc 660  
 cttacgttcc cgttcttgaa aactttcact aaagggttg ttgtcatcaa attctaccg 720  
 agtggtgkx tcactctgtg gatttgcatt tgagactgtc cctggggctg gtgtacaagt 780

|            |             |             |            |            |             |      |
|------------|-------------|-------------|------------|------------|-------------|------|
| ttttattggt | aactgggcaa  | ttgggggctg  | aattctagga | ggattgaggg | gcaggtgggc  | 840  |
| agragcactg | ttgggttgcc  | atccaggtaa  | actgggcatt | ctaacagggc | tagtatggcc  | 900  |
| agaaataact | gttggtgtgct | gctgggtgctg | aagctgctgt | ggcaccatgg | gaaaggtggg  | 960  |
| ttggctcatg | gtgggtggag  | tggcacctgg  | aattaggggt | ggctggggct | ggacactggg  | 1020 |
| catcatggta | gggtggggcca | ttgcacattg  | ctgctgctgt | ttgatccgat | aatcttcaat  | 1080 |
| caattcagca | tgttctttct  | gttgtttacg  | aatctgttct | agctgtttct | gaaccatgct  | 1140 |
| ttgctgttca | gtaacatgct  | tgagttgttc  | tgcattcttc | tctggaaatt | cacgcccagc  | 1200 |
| tttcttggca | gtacgttgtt  | tagctgaaag  | ggccttctta | gattttctgt | gagcaccaat  | 1260 |
| ttgttcttca | agatacttct  | gctgcatttg  | aagcagctgt | tgggtctcct | ggrgcccactc | 1320 |
| ttcatactgc | ttacgctgtg  | aatcattgac  | aaagccggga | ccaaaattt  |             | 1369 |

&lt;210&gt; 175

&lt;211&gt; 2379

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1881)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 175

|             |             |            |             |             |             |      |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| ggcagagcta  | gtgtggactc  | catccccctg | gagtgggatac | acgnctatga  | cctcagtcgg  | 60   |
| gacctggagt  | ctgcaatgtc  | cagagctctg | ccctctgagg  | atgaagaagg  | tcaggatgac  | 120  |
| aaagatttct  | acctccgggg  | agctgttgsc | ttatcagggg  | accacagtgc  | cctagagtca  | 180  |
| cagatccgac  | aactgggcaa  | agcctggatg | atagccgctt  | tcagatacag  | caaaccgaaa  | 240  |
| atatcattcg  | cagcaaaact  | cccacggggc | cggagctaga  | caccagctac  | aaaggctaca  | 300  |
| tgaactgct   | ggcggaatgc  | agtagcagta | tagactccgt  | gaagagactg  | gagcacaac   | 360  |
| tgaaggagga  | agaggagagc  | cttctgggct | ttgttaacct  | gcatagtacc  | gaaaccgaaa  | 420  |
| cggctgggtg  | gattgaccga  | tgggagcttc | tccaggccca  | ggcattgagc  | aaggagttag  | 480  |
| ggatgaagca  | gaacctccag  | aagtggcagc | agtttaactc  | agacttgaac  | agcatctggg  | 540  |
| cctggctggg  | ggacacggag  | gaggagttag | aacagctcca  | gcgtctggaa  | ctcagcactg  | 600  |
| acatccagac  | catcgagctc  | cagatcaaaa | agctcaagga  | gctccagaaa  | gctgtggacc  | 660  |
| accgcaaaagc | catcatcctc  | tccatcaatc | tctgcagccc  | tgagttcacc  | caggctgaca  | 720  |
| gcaaggagag  | ccgggacctg  | caggatcgct | tgtsgcagat  | gaatgggcgc  | tgggaccgag  | 780  |
| tgtgctctct  | gctggaggag  | tggcggggcc | tgctgcagga  | tgccctgatg  | cagtgccagg  | 840  |
| gtttccatga  | aatgagccat  | ggtttgcttc | ttatgctgga  | gaacattgac  | agaaggaaaa  | 900  |
| atgaaattgt  | ccctattgat  | tctaaccttg | atgcagagat  | acttcaggac  | catcacaac   | 960  |
| agcttatgca  | aataaagcat  | gagctgttgg | aatcccaact  | cagagtagcc  | tctttgcaag  | 1020 |
| acatgtcttg  | ccaactactg  | gtgaatgctg | aaggaaacaga | ctgtttagaa  | gccaaagaaa  | 1080 |
| aagtccatgt  | tattggaaat  | cggctcaaac | ttctcttgaa  | ggaggtcagt  | cgtcatatca  | 1140 |
| aggaactgga  | gaagttatta  | gacgtgtcaa | gtagtcagca  | ggatttgtct  | tcctgggtctt | 1200 |
| ctgctgatga  | actggacacc  | tcagggtctg | tgagtccay   | atcaggaagg  | agcaccgcaa  | 1260 |
| acagacagaa  | aacgccacga  | ggcaagtgtg | gtctctcaca  | gcctggaccc  | tctgtcagca  | 1320 |
| gtccacatag  | cagggtccaca | aaagggtggc | ccgattcctc  | cctttctgag  | ccarggccag  | 1380 |
| gtcgggtccg  | ccgcgggttc  | ctgttcagag | tcctccgagc  | agctcttccc  | cttcagcttc  | 1440 |
| tcctgtctct  | cctcatcggt  | ctgtccctgc | ttgtaccaat  | gtcagaggaa  | gactacagct  | 1500 |
| gtgcctctc   | caacaacttt  | gcccggtcat | tccaccccat  | gctcagatac  | acgaatggcc  | 1560 |
| ctcctccact  | ctgaactaag  | cagatgccat | ctgcagaagt  | gctggttagca | taaggaggat  | 1620 |
| cgggtcataa  | gcaatcccaa  | actaccaaca | agaggacctt  | gatcttggcg  | aaagccmtcg  | 1680 |
| gtgtggcagc  | tttagcctcc  | tccagatcac | atgtgtgcaa  | attatggctt  | cagaggtgga  | 1740 |
| agataaacag  | tgacggggga  | acaaacagac | aacaagaagg  | tttgaagaa   | atctggtttg  | 1800 |

|             |             |             |            |            |            |      |
|-------------|-------------|-------------|------------|------------|------------|------|
| agactctgaa  | ccttagcact  | aaggagattg  | agtaaggacc | tccaaagttc | cccggactca | 1860 |
| tgaattcttg  | gcccttggcc  | nattctgtgc  | acagccaagg | acttcagtag | accatctggg | 1920 |
| cagctttccc  | atgggtgctgc | tccaaccatc  | agataaatga | ccctcccaag | caccatgtca | 1980 |
| gtgtcgtaca  | atctaccaac  | caaccagtgc  | tgaagagatt | ttagaacctt | gtaacataca | 2040 |
| atttttaaga  | gcttatatgg  | cagcttcctt  | tttaccttgt | tttccttttg | ggcatgatgt | 2100 |
| tttaaccttt  | gctttagaag  | cacaagctgt  | aaatctaaaa | ggcacttttt | tttagaggta | 2160 |
| taaagaaaaa  | ctagatgtaa  | taaataagat  | catggaaggc | tttatgtgaa | aaaagttgaa | 2220 |
| tggttatagta | aaaaaaaaag  | atatttatgt  | atgtacagtt | tgctaaagcc | aagttttgtt | 2280 |
| tgtattgatt  | tctttgcatt  | tattatagat  | attataaaat | aaaaaaaaaa | aaaaaaaaac | 2340 |
| tcgagggggg  | gcccgggtacc | caattcgtccc | tatagttag  |            |            | 2379 |

&lt;210&gt; 176

&lt;211&gt; 1348

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (407)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (408)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1331)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 176

|             |            |            |             |            |             |      |
|-------------|------------|------------|-------------|------------|-------------|------|
| gcgccttcac  | gatgccggcg | gtcagtggtc | caggctccctt | attctgcctt | ctcctcctgc  | 60   |
| tccctggacc  | ccacagccct | gagacggggg | gtcctcctct  | acgcaggttt | gagtacaagc  | 120  |
| tcagcttcaa  | aggcccaagg | ctggcattgc | ctgggggctg  | aatacccttc | tggagccatc  | 180  |
| atggagggtga | ggggcagggg | tgggggaccg | tatgccccag  | gtccctcaaa | gtgctggagg  | 240  |
| ggctgtract  | tggtggggag | tggtgtctgc | acagccatcc  | tctgtccagg | gtggggcaag  | 300  |
| gcctgggaca  | gtgccaggca | ccccaggacc | ccttccaggc  | ttgtctcctg | ctccaccgcc  | 360  |
| tcaacacccc  | ccaccctgc  | ccaagctggt | tctcctctgc  | ctctctnntt | ccctgcccc   | 420  |
| ggactttctt  | cttctcctct | gcctctcctt | ggacccctgc  | ccttcctcta | cctctgacct  | 480  |
| gtgaacacac  | agacacatgc | tcacacacta | agtccccarg  | acacmsaaag | gcaatgtgga  | 540  |
| ccagcacaaa  | cctccactct | cccggtccca | tcccarcggg  | cctgtggctg | gccatgaaaa  | 600  |
| ctggggggcta | cctggaggga | agcatcctca | tcccagggtga | gtgggcacca | gcccttcctt  | 660  |
| gtatgtgtgt  | tgtgggtgga | agcaggcatg | agagcatctt  | agcccatagg | tttgtattca  | 720  |
| gggactttcca | aaccagacc  | tacaaagagt | gtgtcttcta  | ccagatcttg | ttcaaaaaag  | 780  |
| ggtttgtgat  | gatggaacta | cacgatagag | ggagttagca  | agaacaatga | ggattagagt  | 840  |
| ggagcgtgaa  | atagtctagg | agcatggctt | ccaaaacata  | tgctgtgagg | tctgtccacc  | 900  |
| tgagagttgg  | gccatggatt | taattctgag | cctcttagca  | ggcaaagcaa | agacagaaag  | 960  |
| cagatcgggt  | gtggatttct | gtctataaaa | tgtgagttct  | tggccgggtg | cggtgggtca  | 1020 |
| cgcctgtaat  | cccggcgctt | tgggaggcca | ggcgggatgg  | gtcgcgaggt | caggagggtt  | 1080 |
| gaaaccatcc  | tggccggaat | ggtgaagccc | tgactctact  | agaagtgcaa | agattggctg  | 1140 |
| ggtgtggtgg  | cgtgcgcctg | tggtcccagc | ttctcgggag  | gctgaggcgg | gagagttgct  | 1200 |
| tgggcctggg  | aggccgaggt | tgcggtgagc | tgagatcctg  | ccattgcact | tcagccctgg  | 1260 |
| caagagacca  | gactctggct | caaaaaaaaa | aaaaaaaaaa  | actcgagggg | ggcccggtacc | 1320 |
| caattcgccg  | natatgatcg | taaacaaat  |             |            |             | 1348 |

<210> 177  
 <211> 1502  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (446)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (470)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1024)  
 <223> n equals a,t,g, or c

<400> 177  
 ctcaaaataa ataaataaat aaaaatttgt attccattga tttgggtaga caccaggaat 60  
 gtgcatttct aacaagcttt ccaggcgatc ctatagtaag tcatctgtgg actacttta 120  
 gaaactcttc tatagagaat ggagttggat taataatagg tgatttttta cactggactg 180  
 attcacaaga acctaaacag tagtccatga agctgctcat ctgtggtaac tatttgccc 240  
 cgtctcactc tgaaagcagc aggagatgtt gtttactttg tttctatccc ctttgtctgg 300  
 agattaattt tggaatgaaa gtttttctct ctatgccatt cctggttctt ttccaaagcc 360  
 tcatacaaga ggattaggtc acaatgcatg cattaccttt taaaagaatg cgatattgat 420  
 accgatgctt actttttttt tttttnacta cttgttttat tcttccagn aaagtatagc 480  
 ccgcctttct atagcatagt tctctttagg tggaatgatt cctataagat ttctcattat 540  
 taaatcatgc atttttcaag atggaatcaa tmtttgattt aatctaagct gatattctca 600  
 tttgttagaa gaacaaccta catgctagag agagaggagg aaatataccc acgaccacac 660  
 agccagtttag tatccagttg gtgctggact ccagccaggt gtcctgcctc atggtagtta 720  
 aatgatatat agaaaaggta aatttttaaa gaaatattta ttaatatatt cctataaaac 780  
 attttaaagg taaccacata aaaatgggta atttttccat tccaaagtaa atgctaagca 840  
 tgtttattaa tgaagcagta cttctgatta gtatatgaca ttctgaagtt aattaaactc 900  
 attgacttaa atgtgtcttc cttggtatag tggaggattt gaggattgga atatatagta 960  
 gagtgcttgc ttaagcctgg gagcccatct ttatagctat ttgatgtaag aaaagagaca 1020  
 tggncattt cttaaactata taaggtagt gtgtctatcc ccagcagata taaaggaana 1080  
 aggaactttt tttgattccc acctcccag cctcacctag ccactctcca gcctcaaata 1140  
 tagagatgtt agtgcaaggc cctgggctct aggtgatcat ttcataagtc ctttacagat 1200  
 aaagaaaaag tagtgtttgt atgtttgttt ttaagtaacc ccaaaacaaa tttatattgt 1260  
 attcagcaaa attggaattc aggtgtttta ttttagaaca tgaagtgcct gctgttttaa 1320  
 gcattgactt gtataaaaag aattgcatgt ctccagtaag cttatgggtt ttctcatttt 1380  
 taggtatatg gcttttaatc atgtaaagtg aaacattagt tttcttgcat tttattacag 1440  
 gttctttgtt gcaataaaga tgctgctgaa attaattgaa aaaaaaaaaa aaaaaaactc 1500  
 ga 1502

<210> 178  
 <211> 1637  
 <212> DNA  
 <213> Homo sapiens

<400> 178  
 attttctagc ccacaaggac tgaagttcag atccaaaagt tcacttgcta attatcttca 60  
 caaaaatgga gagacttctc ttaagccaga agattttgat tttactgtac tttctaaaag 120  
 gggatatcaag tcaagatata aagactgcag catggcagcc ctgacatccc atctacaaaa 180



|             |             |             |             |            |            |      |
|-------------|-------------|-------------|-------------|------------|------------|------|
| ccaaagtaac  | aattcaaact  | ggaacctcag  | gacccgaagc  | aagtgcacaa | aggatgtggt | 240  |
| tatgccgcc   | agtagtagtt  | cagagttgca  | ggagagcaga  | ggactctcta | actttacttc | 300  |
| cactcatttg  | cttttgaaag  | aagatgaggg  | tggtgatgat  | gttaacttca | gaaaggtag  | 360  |
| aaagcccaaa  | ggaaagggtga | ctattttgaa  | aggaatccca  | attaagaaaa | ctaaaaaagg | 420  |
| atgtaggaag  | agctgttcag  | gttttggtcm  | aagtgatagc  | aaaagagaat | ctgtgtgtaa | 480  |
| taaagcagat  | gctgaaagtg  | aacctgttgc  | acaaaaaagt  | cagcttgata | gaactgtctg | 540  |
| cattttctgat | gctggagcat  | gtggtgagac  | cctcagtgtg  | accagtgaag | aaaacagcct | 600  |
| tgtaaaaaaa  | aaagaaagat  | cattgagttc  | aggatcaaata | ttttgttctg | aacaaaaaac | 660  |
| ttctggcatc  | ataaacaata  | tttgttcagc  | caaagactca  | gaacacaacg | agaagtatga | 720  |
| ggataccttt  | ttagaatctg  | aagaaatcgg  | aacaaaagta  | gaagttgtgg | aaaggaaaga | 780  |
| acattttgcat | actgacattt  | taaaacgtgg  | ctctgaaatg  | gacaacaact | gctcaccaac | 840  |
| caggaaagac  | ttcactgaag  | ataccatccc  | acggaacaca  | gatagaaaga | aggaaaaaaa | 900  |
| gcctgtattt  | ttccagcaaa  | tataacaaag  | aagctcttag  | ccccccacga | cgtaaagcct | 960  |
| ttaagaaatg  | gacacctcct  | cgggtcacctt | ttaatctcgt  | tcaagaaaca | ctttttcatg | 1020 |
| atccatggaa  | gcttctcatc  | gctactatat  | ttctcaatcg  | gacctcaggc | aaaatggcaa | 1080 |
| tacctgtgct  | ttggaagttt  | ctggagaagt  | atccttcagc  | tgaggtagca | agaaccgcag | 1140 |
| actggagaga  | tgtgtcagaa  | cttcttaaac  | ctcttggtct  | ctacgatctt | cgggcaaaaa | 1200 |
| ccattgtcaa  | gttctcagat  | gaatacctga  | caaagcagtg  | gaagtatcca | attgagcttc | 1260 |
| atgggattgg  | tgcaccttga  | agaccacaaa  | ttaaataaat  | atcatgactg | gctttgggaa | 1320 |
| aatcatgaaa  | aattaagtct  | atcttaaaact | ctgcagcttt  | caagctcatc | tgttatgcat | 1380 |
| agctttgcac  | ttcaaaaaag  | cttaattaag  | tacaaccaac  | cacctttcca | gccatagaga | 1440 |
| ttttaattag  | cccaactaga  | agcctagtgt  | gtgtgctttc  | ttaatgtgtg | tgccaatggt | 1500 |
| ggatctttgc  | tactgaatgt  | gtttgaacat  | gttttgagat  | ttttttaaaa | taaattatta | 1560 |
| tttgacaaca  | atccaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa | aaaaaaaaaa | 1620 |
| aaaaaaaaaa  | aaaaaaa     |             |             |            |            | 1637 |

&lt;210&gt; 179

&lt;211&gt; 2911

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (622)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 179

|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| ggtggttttt  | gttctgcaat  | aggcggctta  | gagggagggg  | ctttttcgcc | tatacctact  | 60   |
| gtagcttctc  | cacgtatgga  | ccctaaaggc  | tactgctgct  | actacggggc | tagacagtta  | 120  |
| ctgtctcagc  | tctaggatgt  | gcgttcttcc  | actagaagct  | cttctgaggg | aggtaattaa  | 180  |
| aaaacagtgg  | aatggaaaaa  | cagtgtctgta | gtcatcctgt  | aatatgctcc | ttgtcaacaa  | 240  |
| tgtatacatt  | cctgctaggt  | gccatattca  | ttgctttaag  | ctcaagtcgc | atcttactag  | 300  |
| tgaagtattc  | tgccaatgaa  | gaaaacaagt  | atgattatct  | tccaactact | gtgaatgtgt  | 360  |
| gctcagaact  | ggtgaagcta  | gttttctgtg  | tgcttgtgtc  | attctgtgtt | ataaagaaag  | 420  |
| atcatcaaag  | tagaaaattg  | aaatatgctt  | cctggaagga  | attctctgat | ttcatgaagt  | 480  |
| ggtccattcc  | tgccctttctt | tatttccctgg | ataacttgat  | tgtcttctat | gtcctgtcct  | 540  |
| atcttcaacc  | agccatggct  | gttatcttct  | caaatttttag | cattataaca | acagctcttc  | 600  |
| tattcaggat  | agtgtctgaag | angcgtctaa  | actggatcca  | gtgggcttcc | ctcctgactt  | 660  |
| tatttttgtc  | tattgtggcc  | ttgactgccg  | ggactaaaaac | tttacagcac | aacttggcag  | 720  |
| gacgtggatt  | tcatacagat  | gcctttttca  | gcccttccaa  | ttcctgcctt | cttttcagaa  | 780  |
| atgagtgtcc  | cagaaaagac  | aattgtacag  | caaagggaatg | gacttttctc | gaagctaaat  | 840  |
| ggaacaccac  | agccagagtt  | ttcagtcaca  | tccgtcttgg  | catgggccat | gttcttatta  | 900  |
| tagtccagtg  | ttttatttct  | tcaatggcta  | atatctataa  | tgaaaagata | ctgaagggaag | 960  |
| ggaaccagct  | cactgaargc  | atcttcatac  | agaacagcaa  | actctatttc | tttggcattc  | 1020 |
| tgtttaaatg  | gctgactctg  | ggccttcaga  | ggagtaaccg  | tgatcagatt | aagaactgtg  | 1080 |
| gattttttta  | tggccacagt  | gcattttcag  | tagcccttat  | ttttgtaact | gcattccagg  | 1140 |
| gccttttcagt | ggcttttcatt | ctgaagttcc  | tggataacat  | gttccatgtc | ttgatggccc  | 1200 |

|             |            |             |             |            |             |      |
|-------------|------------|-------------|-------------|------------|-------------|------|
| aggttaccac  | tgtcattatc | acaacagtgt  | ctgtcctggg  | ctttgacttc | aggccctccc  | 1260 |
| tggaatTTTT  | cttgggaagc | ccatcagtc   | ttctctctat  | atTTatTTat | aatgccagca  | 1320 |
| agcctcaagt  | tccggaatac | gcacctaggc  | aagaaaggat  | ccgagatcta | agtggcaatc  | 1380 |
| tttgggagcg  | ttccagtggg | gatggagaag  | aactagaaa   | acttaccaaa | cccaagagt   | 1440 |
| atgagtcaga  | tgaagatact | ttctaactgg  | taccacata   | gtttgcagct | ctcttgaacc  | 1500 |
| ttatTTTcac  | atTTTcagtg | tttgtaatat  | ttatctTTTc  | actTTgataa | accagaaatg  | 1560 |
| tttctaaatc  | ctaataTTct | ttgcataat   | ctagctactc  | cctaaatggg | tccatccaag  | 1620 |
| gcttagagta  | cccaaaggct | aagaaattct  | aaagaactga  | tacaggagta | acaatatgaa  | 1680 |
| gaattcatta  | atatctcag  | acttgataaa  | tcagaaagtt  | atatgtgcag | attatTTTcc  | 1740 |
| ttggccttca  | agcttccaaa | aaacttgtaa  | taatcatgtt  | agctatagct | tgtatataca  | 1800 |
| catagagatc  | aatttgccaa | atattcaca   | tcagttagtt  | ctagtttaca | tgccaaagtc  | 1860 |
| ttccctTTTT  | aacattataa | aagctagggt  | gtctcttgaa  | TTTTgaggcc | ctagagatag  | 1920 |
| tcattTTtgca | agtaaagagc | aacgggaccc  | TTTctaaaaa  | cgTTggTTga | aggacctaaa  | 1980 |
| tacctggcca  | taccatagat | ttgggatgat  | gtagtctgtg  | ctaaatattt | tgctgaagaa  | 2040 |
| gcagTTTctc  | agacacaaca | tctcagaatt  | TTaattTTTta | gaaattcatg | ggaaattgga  | 2100 |
| TTTTTgtaat  | aatctTTTga | TgTTTTaaac  | attggTTccc  | tagtcaccat | agttaccact  | 2160 |
| TgtatTTTaa  | gtcattTTaa | caagccacgg  | TggggctTTT  | ttctcctcag | TTtgaggaga  | 2220 |
| aaaatcttga  | Tgtcattact | cctgaattat  | tacattTTTgg | agaataagag | ggcattTTTat | 2280 |
| TTtattagtt  | actaattcaa | gctgtgacta  | TTgtatatct  | TTccaagagt | Tgaaatgctg  | 2340 |
| gcttcagaat  | cataccagat | Tgtcagtga   | gctgatgcct  | aggaaactTT | aaagggatcc  | 2400 |
| TTTcaaaagg  | atcacttagc | aaacacatgt  | TgactTTTaa  | ctgatgtatg | aatattaata  | 2460 |
| ctctaaaaat  | agaaagacca | gtaatatata  | agtcactTTa  | cagtgcact  | tcacacttaa  | 2520 |
| aagtgcattg  | tattTTTcat | ggTattTTTgc | atgcagccag  | TTaactctcg | tagatagaga  | 2580 |
| agtcaggTga  | tagatgatat | Taaaaattag  | caaacaaaag  | TgactTgctc | agggTcatgc  | 2640 |
| agctgggTga  | Tgatagaaga | gtgggctTTa  | actggcaggc  | ctgtatgTTT | acagactacc  | 2700 |
| atactgtaaa  | TatgagctTT | atggTgtcat  | Tctcagaaac  | TTatacatTT | ctgctctcct  | 2760 |
| ttctcctaag  | TTTcatgcag | atgaatata   | ggtaatatac  | Tattatataa | TTcattTgtg  | 2820 |
| atatccacaa  | Taatatgact | ggcaagaatt  | ggTggaatt   | Tgtaattaaa | ataattatta  | 2880 |
| aacctaaaaa  | aaaaaaaaa  | aaaaactcga  | g           |            |             | 2911 |

&lt;210&gt; 180

&lt;211&gt; 519

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 180

|            |            |            |             |            |             |     |
|------------|------------|------------|-------------|------------|-------------|-----|
| ggcacgagcc | ccaggccagc | cagggccagg | cctactTTTgg | ccacccttaa | attagaatgt  | 60  |
| ggggTcaggg | gtcacagaaa | agccattTct | ctgacctagt  | gtttggcgTc | cgggaaactct | 120 |
| gtgcccaccc | ttcagaccct | ggcagTcctc | actgaggcca  | ttggcccaga | gcccgcctatc | 180 |
| ccccgaracc | cccgggagcc | gcctgtTgCc | acgtccacac  | ctgccacacc | ctctgccggg  | 240 |
| ccccagcccc | tcccacccgg | gaccgtgctg | gtccctgggg  | gtcctgcccc | acctTgcctt  | 300 |
| ggggaggcat | gggccctcct | cctccacccc | Tgccggccgt  | cactcacctc | ttgcttctgg  | 360 |
| tccccagggc | ctagcccttg | gaaggagaca | ggagtctagg  | gaggctgaag | cccactcccg  | 420 |
| gggaggcccc | Tgtcctccca | gccccaggga | cagcaaggaa  | aagagaagag | agcagagcat  | 480 |
| ttcatggctc | Taataaaaaa | aaaaaaaaa  | aaaactcga   |            |             | 519 |

&lt;210&gt; 181

&lt;211&gt; 968

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (45)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (135)  
 <223> n equals a,t,g, or c

<400> 181  
 tccccctggg gccggaaaaa gcgggggttg cctgnccatt ggtnntccat gccgcccggc 60  
 catgccccag tactagcctg cagtcccaat gtageccctc cctcytcama gagcccytcm 120  
 aaccgccccg stcanttgtg atttcaggag gatttgatga agatgttaaa gcgaaagtgg 180  
 agaaccttct cgggatttcc agcctggaaa aaacggaccc tggtaggcaa gcaccctgca 240  
 gccctccctg tccccctctt cccctccctt tcycccgccc gtggagacag ctgttytcag 300  
 cagggctctc cgcagggagg ggcccggtc cttccctggc agcaacatcc ttgcccttgt 360  
 cacacaagtc agcctccatc tgcgcagctc tgtggatgcg ctgctggagg gcaacaggta 420  
 tgtcactggc tggttcagcc cctaccaccg ccagcggaaag ctcattccacc cggtcattggt 480  
 tcagcacatc cagcccgag cgctcagcct cctggcacag tggagcacc tcgtgcagga 540  
 gctggaggct gccctgcagc tggttttcta cccggatgcc gtggaggagt ggctggagga 600  
 aaacgtgcac cccagcctgc agcggctgca arctctgtc caggacctca gcgaggtgtc 660  
 tgcccccccg ctgccacca ccagccctgg cagggacgtt gctcaggacc cctgagggga 720  
 gagctcatgc cagggggctc ctgctggagg ctgggggggc tctgcwytky cwwwtggcct 780  
 gggcaatacg gccacgtgg gcgtcgtgcc ctctggccca gcagtgtctt gccacactc 840  
 agttcctgag ggccctgggc agccctggg ggagagacta gaaaacacag aaggaagcag 900  
 cacagggaga ccgcctttgt gatctgcagc tgtgacactg attctttgga aataaagagt 960  
 ggaagctg 968

<210> 182  
 <211> 1128  
 <212> DNA  
 <213> Homo sapiens

<400> 182  
 tgtaaaagt atcagtaatc ctaattcttt tcctggggtt tccttttgtc acttattaat 60  
 cagtttttga aaggacgaat gaatttagag atgtactctg gagcagtatc atgttaaacc 120  
 aggggtatat tagaaaaatc atcctcataa tcattctggg aagtttttcc tccccaaaaa 180  
 aagccatcct gatgggtttt caaaaccaga aaaaagctct taatgaggaa cagaccactg 240  
 gagtaccat gagcatctca ggaaaactga gaccctcgag aagccttgat ttcgtgcaac 300  
 ccccaagggt tcagagccag cagcccagtg ctgtggttga cagacgtggt tttktggrga 360  
 aagcagccag aggccaggaa ttttcagagt cgtgagtcac grtytcccac ccaagattag 420  
 agcamagatt agccatactg agatttggtt aaatcattct gtctaagcaa tggaggtgtg 480  
 tgcamacgtg cagtgcctgt tcacagggga tgcaggcaga tcsygggttt aggatggggr 540  
 aggccaccgc acccccyttc aytgctctgc acctgctccc tcacgtggac actgtccaca 600  
 actgtggctc tcacaggaca gttgcccaag gagctcatat cttattggag ataggggggtc 660  
 gtacaggtga cattcatgag cagtgtgagc cgggtgacat gggggtgtca acccagcatc 720  
 tgtccaggag ctccctcctgc agcggctctg gcagggtggc tgaggctcct ttttgagaga 780  
 gaactgtttg gccttcctgt ctccctcctc ctgactctgt ctttcttgga acaccacca 840  
 agaacgtcac ctccctccatc agattgtgag ctcctggagg gcaggagctg tgtccttcta 900  
 ttcatcttcc tatccccaga accttgccca gatcctggaa tgtggtaggt gctcagtaaa 960  
 tgttgtttga ataaatgaat gaatgaatga acaaatgaat gaatttgctt acttcaaggc 1020  
 aaaagaacca tgaaactgta ttttgagttt ctatgttata gcagtcagca aatcctatta 1080  
 aatactttgt gtttccaagc aaaaaaaaaa aaaaaaaaaa aaactcga 1128

<210> 183

&lt;211&gt; 2276

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 183

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ccgcggcgctc | tgacctcatg  | gcgtagagcc  | tagcaacagc  | gcaggctccc  | agccgagtcc  | 60   |
| ggtatggccg  | ctgccgtccc  | gaagaggatg  | agggggccag  | cacaagcgaa  | actgctgccc  | 120  |
| gggtcggcca  | tccaagccct  | tgtgggggtg  | gcgcggccgc  | tggctctggc  | gctcctgctt  | 180  |
| gtgtccgcg   | ctctatccag  | tgttgatca   | cggactgatt  | caccgagccc  | aaccgtactc  | 240  |
| aactcacata  | tttctacccc  | aaatgtgaat  | gctttaacac  | atgaaaacca  | aaccaaacct  | 300  |
| tctatttccc  | aaatcagcac  | caccctccct  | cccacgacga  | gtaccaagaa  | aagtggagga  | 360  |
| gcatctgtgg  | tccctcatcc  | ctgcctact   | cctctgtctc  | aagaggaagc  | tgataacaat  | 420  |
| gaagatccta  | gtatagagga  | ggaggatctt  | ctcatgctga  | acagttctcc  | atccacagcc  | 480  |
| aaagacactc  | tagacaatgg  | cgattatgga  | gaaccagact  | atgactggac  | cacggggccc  | 540  |
| agggacgacg  | acgagtctga  | tgacaccttg  | gaagaaaaca  | ggggttacat  | ggaaattgaa  | 600  |
| cagtcaagtga | aatcttttaa  | gatgccatcc  | tcaaatatag  | aagaggaaga  | cagccatttc  | 660  |
| ttttttcatc  | ttttattttt  | tgttttttgc  | attgctgttg  | tttacattac  | atatcacaac  | 720  |
| aaaaggaaga  | tttttcttct  | ggttcaaagc  | aggaaatggc  | gtgatggcct  | ttgttccaaa  | 780  |
| acagtggaaat | accatcgccct | agatcagaat  | gttaatgagg  | caatgccttc  | tttgaagatt  | 840  |
| accaatgatt  | atatttttta  | aagcactgtg  | atttgaattt  | gcttatgtaa  | ttttatttgc  | 900  |
| ttgacttttt  | atatgatatt  | gtgcaaatgt  | ttgccatagg  | caattggtac  | ttaaatgaga  | 960  |
| ggtgagtctc  | tctttttgcct | tgggtgctttg | gaaattaaat  | gtcacaacg   | agtatataat  | 1020 |
| tttttatctg  | tacttttaga  | gctgagttta  | atcagggtgc  | caaaatgtga  | gttaaaccatt | 1080 |
| accttatatt  | tacactgtta  | gtttttattg  | tttttagattt | attatgcttc  | ttctggaagt  | 1140 |
| attagtgatg  | ctacttttaa  | aagatcccaa  | acttgtaact  | aaattctgac  | atatctgtta  | 1200 |
| ctgctgactc  | acattcattc  | tccgccattc  | aaatactatt  | ttttatccac  | atTTTTTTTT  | 1260 |
| gttcccaaac  | tgtaatgtac  | aaggatatgt  | gtgataatgc  | tttggatttg  | agtaatatatt | 1320 |
| ttttttcttc  | caagaaaact  | gctttggata  | tttttagata  | atttaaacad  | aatttaggat  | 1380 |
| aatgatattg  | ctcaatctga  | ccacaatttt  | aggtaaaaca  | ttaaatgtgt  | cagaaatctt  | 1440 |
| ggcaacagag  | actctgcagc  | ttgcagtggg  | catagataaa  | atgttacaga  | gatactattt  | 1500 |
| ttttggttgg  | aattactata  | ttaaatttag  | aagcagaaac  | tggtaaaatg  | ttaaatacat  | 1560 |
| gtacaattgc  | ttttagttag  | caattgattg  | tagcatgggt  | tcctccaagg  | tttcaagcaa  | 1620 |
| tgggcagagt  | ttaaaattat  | atcagattcg  | tttacttcgt  | ttattatttt  | acagtaaatt  | 1680 |
| tgaataaatc  | ttaggggtca  | ttatcactta  | aataatactg  | tacctaggtc  | tttcaaatta  | 1740 |
| aaattatacc  | tgaatgaagt  | tgtttgtata  | cataaaggat  | atttgtgtac  | aattaccttt  | 1800 |
| tttcccccac  | acttgttttc  | tttgtttttg  | ttttttatgg  | caactggaaa  | gtattttacta | 1860 |
| tgggattcat  | ttatgtctgt  | ctttctatca  | taaagaattg  | atcaatatgt  | aaatatgtga  | 1920 |
| tttgaaccat  | ggttgactta  | caagtgtcac  | tacagctttt  | tagaaaacat  | agccctaata  | 1980 |
| tatgttaagc  | aggaccgggg  | tgagccagtg  | ggcttgcgct  | ttatgtagag  | ctggaagaag  | 2040 |
| gccgtccatc  | ctgtctcttg  | ggcggacagt  | gtacttttct  | aataggggaag | ggaagcacaa  | 2100 |
| tggaaatacc  | cctgaaccgt  | tttattgcag  | taattttttt  | catatctgaa  | actattattt  | 2160 |
| aatattttga  | ataagatttt  | aaaaataaaa  | tggcaagat   | ataaatctaa  | aaaaaaaaaa  | 2220 |
| aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaa      | 2276 |

&lt;210&gt; 184

&lt;211&gt; 3374

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 184

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| ggcggcagtg  | tccaagctac | gccactcggg | ctggggcggt | gggagcggga | gtgcagagcg | 60  |
| tggctcgtggc | ggcggcggtg | agaagagcga | ggcggaggag | ggggtgccat | ggccgggcag | 120 |
| cagttccagt  | acgatgacag | tgggaacacc | ttcttctact | tcctcacctc | cttcgtgggg | 180 |
| ctcatcgtga  | tcccggcgac | atactacctc | tggccccgag | atcagaatgc | cgagcaaatt | 240 |
| cgattaaaga  | atatcagaaa | agtatatgga | aggtgatgtg | ggatcgttt  | acggttatta | 300 |
| aaaccccagc  | caaatattat | tcctacagta | aagaaaatag | ttctgcttgc | aggatgggca | 360 |
| ttgttcttat  | tccttgcata | taaagtttcc | aaaacagacc | gagaatacca | agaatacaat | 420 |

|             |             |            |             |             |             |      |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| ccttatgaag  | tattaaat    | ggatcctgga | gccacagtag  | cagaaattaa  | aaaacaatat  | 480  |
| cgtttgctgt  | cacttaaata  | tcaccagat  | aaaggagggtg | atgagggttat | gttcatgagg  | 540  |
| atagcaaaaag | cttatgctgc  | tttaacggat | gaagagtc    | ggaaaaattg  | ggaagaattt  | 600  |
| ggaaatccag  | atgggcctca  | agccacaagc | tttgaattg   | ccctgccagc  | ttggatagtt  | 660  |
| gaccagaaaa  | attcaattct  | ggttttactt | gtatatggat  | tggcatttat  | ggttatcctt  | 720  |
| ccagttgttg  | tgggctcttg  | gtggtatcgc | tcaatacgct  | atagtggaga  | ccagattcta  | 780  |
| atacgcaaa   | cacagattta  | tacatacttt | gtttataaaa  | cccgaaatat  | ggatatgaaa  | 840  |
| cgtcttatca  | tggttttggc  | tggagcttct | gaatttgatc  | ctcagtataa  | taaagatgcc  | 900  |
| acaagcagac  | caacggataa  | tattctaata | ccacagctaa  | tcagagaaat  | tggcagcatt  | 960  |
| aatttaaaga  | agaatgagcc  | tccacttacc | tgcccatata  | gcctgaaggc  | cagagttctt  | 1020 |
| ttactgtctc  | atcttgctag  | aatgaaaatt | cctgagaccc  | ttgaagaaga  | tcagcaattc  | 1080 |
| atgctaataa  | agtgtcctgc  | cctacttcaa | gaaatggtta  | atgtaatctg  | ccaactaata  | 1140 |
| gtaattggccc | ggaaccgtga  | agaaaggag  | tttcgtgctc  | caactttggc  | atccctagaa  | 1200 |
| aactgcatga  | agctttctca  | gatggccgtt | cagggacttc  | agcaatttaa  | gtctcccctt  | 1260 |
| ctgcagctcc  | ctcatattga  | agaggacaat | cttagacggg  | tttctaatac  | taagaagtat  | 1320 |
| aaaattaaaa  | ctatccagga  | tttggtgagt | ttaaaagaat  | cagatcgtca  | cactctactg  | 1380 |
| cacttccttg  | aagatgaaaa  | atatgaagag | gttatggctg  | tccttgggag  | ttttccatat  | 1440 |
| gtgaccatgg  | atataaaatc  | acaggtgtta | gatgatgaag  | atagcaacaa  | catcacagta  | 1500 |
| ggatccttag  | ttacagtgtt  | ggttaagttg | acaaggcaaa  | caatggctga  | agtattttgaa | 1560 |
| aaggagcagt  | ccatctgtgc  | tgcagaggaa | cagccagcag  | aagatgggca  | gggtgaaact  | 1620 |
| aacaagaaca  | ggacaaaagg  | aggatggcaa | cagaagagta  | aaggacccaa  | gaaaactgct  | 1680 |
| aatcaaaaa   | aaaagaaacc  | tttaaaaaaa | aaacctacac  | ctgtgctatt  | accacagtca  | 1740 |
| aagcaacaga  | aacaaaagca  | ggcaaatgga | gtcgttggga  | atgaagctgc  | agtaaggaa   | 1800 |
| gatgaagaag  | aagtttcaga  | taagggcagt | gattctgaag  | aagaagaaac  | caatagagat  | 1860 |
| tcccaaagtg  | agaaagatga  | tggtagtgac | agagactctg  | atagagagca  | agatgaaaaa  | 1920 |
| caaaacaaag  | atgatgaagc  | agagtggcaa | gaattacaac  | aaagcataca  | gcgaaaagag  | 1980 |
| agagctctat  | tggaaaccaa  | atcaaaaata | acacatcctg  | tgtatagcct  | ttactttcct  | 2040 |
| gaggaaaaac  | aagaatgggtg | gtggctttac | attgcagata  | ggaaggagca  | gacattaata  | 2100 |
| tccatgccat  | atcatgtgtg  | tacgctgaaa | gatacagagg  | aggtagagct  | gaagtctcct  | 2160 |
| gcaccaggca  | agcctggaaa  | ttatcagtat | actgtgtttc  | tgagatcaga  | ctcctatatg  | 2220 |
| ggtttggtatc | agattaaacc  | attgaagttg | gaagttcatg  | aggctaagcc  | tgtgccagaa  | 2280 |
| aatcaccac   | agtgggatac  | agcaatagag | ggggatgaag  | accaggagga  | cagtgagggc  | 2340 |
| tttgaagata  | gctttgagga  | agaagaggag | gaagaagaag  | atgatgacta  | agcagtactc  | 2400 |
| tgaatggacc  | acagtgtttg  | cacatatttg | caattttttg  | ctgtttttgga | agtgtatcat  | 2460 |
| aaaccagaaa  | cagtacagaa  | ctgatgttga | gggagggtga  | gtttttttac  | tctagaaatg  | 2520 |
| ggtgcataat  | ataactaggc  | agtggcggtg | ccttggtaca  | acctgaaaaa  | tgttaaggct  | 2580 |
| tattgaaacc  | tttcaagtag  | gggatggtag | atttatttca  | tctgcaaatg  | ataataaaatc | 2640 |
| ctttgttatt  | ataactgtcc  | agaagtgtgg | gctatgtatt  | atctgatcag  | tctatggtcc  | 2700 |
| cagtaaaagt  | aaagatgcag  | gaaacacagt | ctgtaaatga  | gcgacttttc  | tttgttcagc  | 2760 |
| tttagtttta  | gcaaaccaca  | caaatatgtt | ttaagtaaca  | tcgctcaagt  | ttaagtaaca  | 2820 |
| tcgctcaagt  | tgataatctc  | ttgataagct | ctggtgttga  | catttttgag  | tgatacaaca  | 2880 |
| gctccactca  | tagattttaa  | cttttatatt | tacttatctt  | ggtcataagt  | tggcattctc  | 2940 |
| tcacattcca  | catgatatag  | agggctacgt | tttggaaattt | tccttttctt  | aattgccag   | 3000 |
| agttatcaga  | cagattataa  | aaatggcttt | taattggctta | aaccatttct  | aaacctctat  | 3060 |
| cttagcagat  | caatgcagga  | tctaattctt | ttgataagtt  | ctagctctaa  | aagtgatagt  | 3120 |
| gggactgtat  | gttttctgat  | actggtggct | tatgttatta  | aacctttttt  | aaaaaagggtt | 3180 |
| cactctaaaa  | gctgaactac  | atccttagtt | ttcagctctac | ttgactctat  | caggagcttt  | 3240 |
| ttaaggaaag  | taagtataac  | atgcaaagga | agcttttttt  | gtattcattt  | tggactcctg  | 3300 |
| tcaataaaaa  | tagaagtttg  | ttgactcgta | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaccc  | 3360 |
| ccgggggggg  | cccc        |            |             |             |             | 3374 |

&lt;210&gt; 185

&lt;211&gt; 1337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

120

&lt;221&gt; SITE

&lt;222&gt; (1337)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 185

|            |             |            |            |            |             |      |
|------------|-------------|------------|------------|------------|-------------|------|
| cttccggttc | tccgggcagc  | tgccactgct | gtagcttctg | ccacctgcc  | cgaccgggccc | 60   |
| tctccctggc | gtttggtcac  | ctctgcttca | ttctccaccg | cgcttatggt | ccctcttgga  | 120  |
| gccagcgtgg | cgggcctggc  | ggctcccggg | tggtgagaga | gcggtccggg | aacgatgaag  | 180  |
| gcctcgagct | gctgctgctg  | tctcagccac | ctcttggtct | ccgtcctcct | cctgctgttg  | 240  |
| ctgctgaac  | taagcgggyc  | cctggmagtc | ctgctgcagg | cagccgaggg | cgccgaggt   | 300  |
| cttgggcctc | ctgaccctag  | accacggaca | ttaccgccgc | tgccaccggg | ccctaccct   | 360  |
| gcccagcagc | cgggcctggg  | tctggctgaa | gctgcggggc | cgccgggctc | cgaggagggc  | 420  |
| aatggcagca | accctgtggc  | cgggcttgag | acggacgac  | acggagggaa | ggccggggaa  | 480  |
| ggctcgggtg | gtggcggcct  | tgtgtgagc  | cccaaccctg | gcgacaagcc | catgaccag   | 540  |
| cgggcctga  | ccgtgttgat  | ggtggtgagc | ggcgcggtgc | tggtgtactt | cgtggtcagg  | 600  |
| acggtcagga | tgagaagaag  | aaaccgaaag | actaggagat | atggagtgtt | ggacactaac  | 660  |
| atagaaaata | tgggaattgac | acctttagaa | caggatgatg | aggatgatga | caacacgttg  | 720  |
| tttgatgcca | atcatcctcg  | aagataagaa | tgtgcctttt | gatgaaagaa | ctttatcttt  | 780  |
| ctacaatgaa | gagtgggaatt | tctatgttta | aggaataaga | agccactata | tcaatgttgg  | 840  |
| gggggtat   | aagttacata  | tattttaaca | acctttaatt | tgtgttgca  | ataaataccg  | 900  |
| tatcctttta | ttatatcttt  | atatgtatag | aagtactctr | ttaatgggct | cagagatggt  | 960  |
| ggggataaag | tatactgtaa  | taatttatct | gtttgaaaat | tactataaaa | cgggtgtttc  | 1020 |
| tgatcgggtt | ttgtttcctg  | cttaccatat | gattgtaaat | tgttttatgt | attaatcagt  | 1080 |
| taatgcta   | tatttttgc   | gatgtcatat | gttaaagagc | tataaattcc | aacaaccaac  | 1140 |
| tggtgtgtaa | aaataattta  | aaatttcctt | tactgaaagg | tatttcccat | ttttgtgggg  | 1200 |
| aaaagaagcc | aaatttatta  | ctttgtgttg | gggtttttta | aatattaaga | aatgtctaag  | 1260 |
| ttattgtttg | caaaaacata  | aatatgattt | taaattctct | taaaaaaaaa | aaaaaaaaac  | 1320 |
| ccgggggggg | gccccggn    |            |            |            |             | 1337 |

&lt;210&gt; 186

&lt;211&gt; 941

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 186

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| ggcacgagcc  | tggacgcagc | agccaccgcc | gggtccctct | ctccacgagg | ctgccggctt | 60  |
| aggaccccc   | gctccgacat | gtcgccctct | ggtcgcctgt | gtcttctcac | catcgttggc | 120 |
| ctgattctcc  | ccaccagagg | acagacgttg | aaagatacca | cgtccagttc | ttcagcagac | 180 |
| tcaactatca  | tggacattca | gggtccgcga | cgagccccc  | atgcagtcta | cacagaactc | 240 |
| cagccccact  | ctccaacccc | aacctggcct | gctgatgaaa | caccacaacc | ccagaccag  | 300 |
| accagcaaac  | tgggaaggaa | ggatgggcct | ctagtgcag  | atccagagac | acacaagagc | 360 |
| accaaagcag  | ctcatccac  | tgatgcac   | acgacgctct | ctgagagacc | atccccagc  | 420 |
| acagacgtcc  | agacagacc  | ccagaccctc | aagccatctg | gttttcatga | ggatgacccc | 480 |
| ttcttctatg  | atgaacacac | cctccggaaa | cgggggctgt | tggtcgagc  | tgtgctgttc | 540 |
| atcacaggca  | tcatcatcct | caccagtggc | aagtgcaggc | agctgtccc  | gttatgccgg | 600 |
| aatcattgca  | ggtgagtcca | tcagaaacag | gagctgacaa | ccygctggg  | acccgaagac | 660 |
| caagccccct  | gccagctcac | cgtgcccagc | ctcctgcac  | ccctcgaa   | gcctggccag | 720 |
| agaggggaaga | cacagatgat | gaagctggag | ccagggtgc  | cgggtccgag | ctcctacctc | 780 |
| ccccaacctt  | gcccgcctt  | gaagctacc  | tggtgctt   | ggggctgtcc | ctcaagttaa | 840 |
| ctcctctgyt  | aagacaaaa  | gtaaagcact | gtggtctttg | caaaaaaaaa | aaaaaaaaaa | 900 |
| aaaaaaaaaa  | aaaaaaaaaa | aaaaaaaaaa | aaaaaactcg | a          |            | 941 |

&lt;210&gt; 187

&lt;211&gt; 678

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 187

|             |             |            |            |             |            |     |
|-------------|-------------|------------|------------|-------------|------------|-----|
| ggcacgaggc  | agcttgtgct  | ttaaaggagg | tgttcaaagc | atgtctgagc  | agagactttt | 60  |
| gggctctgtt  | ttaattaata  | ctttaaaata | attcatattt | aaaatatcag  | atgtttccat | 120 |
| aaagaggagg  | atgttttaaat | gcctccagac | tacattcctt | tttattcttg  | attttacctg | 180 |
| ggagtccaaa  | gttcaattcc  | ataaagcaag | cgtttatttg | tcactttcaa  | tatacatcga | 240 |
| ttgccatgct  | taagatgcaa  | tatgggctgc | ggaaataggt | taaccacacag | gctcccaggg | 300 |
| cccagtgtag  | aagggtgagag | attcgtgtaa | aatgattcaa | ataaaaggaa  | gaccctggcc | 360 |
| gggtgccgta  | gctcacgcct  | gtaatcccag | cactttggga | ggccgaagcg  | agtggatgac | 420 |
| gagggttagga | gttgagagacc | agcctggcca | acatcgtgaa | accccgcttc  | tactaaaaat | 480 |
| acaaaaatta  | gccgggcatg  | gtggcaggca | cctgtaatcc | tagctagtgtg | ggaggtgag  | 540 |
| gcaggagaat  | cgtttgaatc  | tgggagttgg | aggttgcagt | gagctgagat  | cgcgccacag | 600 |
| cactccagcc  | tgggtgacag  | ggtgagactc | tgtctcaaaa | aaaaaaataa  | ataaataaag | 660 |
| taaaaaaaaa  | aaaaaaaaa   |            |            |             |            | 678 |

&lt;210&gt; 188

&lt;211&gt; 1848

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 188

|             |             |            |             |             |            |      |
|-------------|-------------|------------|-------------|-------------|------------|------|
| gaaactggac  | cggagaaccg  | gagcgaagcg | aagcggaaagc | ccggaatgag  | gccggactgg | 60   |
| aaagccggag  | cggggagcag  | cgggcctccc | caaaagcctg  | ccccttcac   | ccagcggaaa | 120  |
| ccgccggccc  | ggccgagcgc  | ggcgcccgct | gcgattgcag  | tcgcggcggc  | ggaggaagag | 180  |
| agacggctcc  | ggcagcggaa  | ccgcctgagg | ctggaggagg  | acaaaccggc  | cgtggagcgg | 240  |
| tgcttggagg  | agctgggtctt | cggcgacgtc | gagaacgacg  | aggacgcgtt  | gctgcggcgt | 300  |
| ctcgagggcc  | cgagggttca  | agaacatgaa | gactcgggtg  | actcagaagt  | ggagaatgaa | 360  |
| gcaaaaaggta | attttccacc  | tcaaaagaag | ccagtttggg  | tggatgaaga  | agatgaagat | 420  |
| gaggaaatgg  | ttgacatgat  | gaacaatcgg | tttcggaagg  | atatgatgaa  | aaatgctagt | 480  |
| gaaagtaaac  | tttcgaaaga  | caaccttaaa | aagagactta  | aagaagaatt  | ccaacatgcc | 540  |
| atgggaggag  | tacctgcctg  | ggcagagact | actaagcggg  | aaacatcttc  | agatgatgaa | 600  |
| agtgaagagg  | atgaagatga  | tttgttgcaa | aggactggga  | atttcatatc  | cacatcaact | 660  |
| tctcttccaa  | gaggcatctt  | gaagatgaag | aactgccagc  | atgcgaatgc  | tgaacgtcct | 720  |
| actgttgctc  | ggaatcccat  | ctgtgcagtt | ccatcccggg  | gcacagattg  | tgatggttgc | 780  |
| tgggattaga  | taatgctgta  | tcactatttc | aggttgatgg  | gaaaacaaat  | cctaaaattc | 840  |
| agagcatcta  | tttggaagg   | tttccaatct | ttaaggcttg  | ttttagtgtc  | aatggggaag | 900  |
| aagttttagc  | cacgagtacc  | cacagcaagg | ttctttatgt  | ctatgacatg  | ctggctggaa | 960  |
| agttaattcc  | tgtgcatcaa  | gtgagaggtt | tgaagagaa   | gatagtgagg  | agctttgaag | 1020 |
| tctcccaga   | tgggtccttc  | ttgtcatata | atggcattgc  | tggatatttg  | catttgctag | 1080 |
| caatgaagac  | caaagaactg  | attggaagca | tgaaaattaa  | tgggaagggtt | gcagcatcca | 1140 |
| cattctcttc  | agatagtaag  | aaagtatacg | cctcttcggg  | ggatggagaa  | gtttatgttt | 1200 |
| gggatgtgaa  | ctcaaggaag  | tgccttaaca | gatttggtga  | tgaaggcagt  | ttatatggat | 1260 |
| taagcattgc  | cacatctagg  | aatggacagt | atggtgcttg  | tggttctaata | tgtggagtgg | 1320 |
| taaatatata  | caatcaagat  | tcttgtctcc | aagaaacaaa  | cccaaagcca  | ataaaagcta | 1380 |
| taatgaactt  | ggttacaggt  | gttacttctc | tgaccttcaa  | tcctactaca  | gaaatcttgg | 1440 |
| caattgcttc  | agaaaaaatg  | aaagaagcag | tcagattggt  | tcactctcct  | tcctgtacag | 1500 |
| tattttcaaa  | cttcccagtc  | attaaaaata | agaatatattc | tcatgttcat  | accatggatt | 1560 |
| tttctccgag  | aagtggatac  | tttgcccttg | ggaatgaaaa  | gggcaaggcc  | ctgatgtata | 1620 |
| ggttgaccca  | ttactcagac  | ttctaagag  | actatttgaa  | gtccagttga  | gtcacaagag | 1680 |
| aagcctgtct  | tgatatatca  | tctcagaaac | tttctctgaat | atgtgataat  | atatggaaaa | 1740 |
| tgatttatag  | atccagctgt  | gcttaagagc | cagtaatgtc  | ttaataaaca  | tgtggcagct | 1800 |
| tttgtttgaa  | aaaaaaaaa   | aaaaaaaaa  | aaaaaaaaa   | aaactcga    |            | 1848 |

&lt;210&gt; 189

&lt;211&gt; 1292

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 189

|             |            |             |            |            |            |      |
|-------------|------------|-------------|------------|------------|------------|------|
| gctgccttgc  | tccacacctg | gtcaggggag  | agaggggaaa | gccaaaggaa | gggacctaac | 60   |
| tgaaaacaaa  | caagctggga | gaagcaggaa  | tctgcgctcg | ggttccgcag | atgcagaggt | 120  |
| tgaggtggct  | gcgggactgg | aagtcatcgg  | gcagaggtct | cacagcarcc | aaggaacctg | 180  |
| gggcccgcctc | ctccccctc  | caggccatga  | ggattctgca | gttaatcctg | cttgctctgg | 240  |
| caacagggct  | tgtaggggga | gagaccagga  | tcatcaaggg | gttcgagtgc | aagcctcact | 300  |
| cccagccctg  | gcaggcagcc | ctgttcgaga  | agacgcggct | actctgtggg | gcgacgctca | 360  |
| tcgccccag   | atggctcctg | acagcagccc  | actgcctcaa | gccccgctac | atagtccacc | 420  |
| tggggcagca  | caacctccag | aaggaggagg  | gctgtgagca | gacccggaca | gccactgagt | 480  |
| ccttccccca  | ccccggcttc | aacaacagcc  | tccccaacaa | agaccaccgc | aatgacatca | 540  |
| tgctggtgaa  | gatggcatcg | ccagtctcca  | tcacctgggc | tgtgcgaccc | ctcaccctct | 600  |
| cctcacgctg  | tgtcactgct | ggcaccagct  | gyctcatttc | cggctggggc | agcacgtcca | 660  |
| gccccagtt   | acgcctgcct | cacaccttgc  | gatgcgccaa | catcaccatc | attgagcacc | 720  |
| agaagtgtga  | gaacgcctac | cccggcaaca  | tcacagacac | catggtgtgt | gccagcgtgc | 780  |
| aggaaggggg  | caaggactcc | tgccaggggtg | actccggggg | ccctctggtc | tgtaaccagt | 840  |
| ctcttcaagg  | cattatctcc | tggggccagg  | atccgtgtgc | gatcaccoga | aagcctggtg | 900  |
| tctacagaa   | agtctgcaaa | tatgtggact  | ggatccagga | gacgatgaag | aacaattaga | 960  |
| ctggaccac   | ccaccacags | ccatcacctc  | ccatttccac | ttggtgtttg | gttcctgttc | 1020 |
| actctgttaa  | taagaaaccc | taagccaaga  | ccctctacga | acattctttg | ggcctcctgg | 1080 |
| actacaggag  | atgctgtcac | ttaataatca  | acctgggggt | cgaatcagct | gagacctgga | 1140 |
| ttcaaattct  | gccttgaaat | attgtgactc  | tgggaatgac | aacacctggg | ttgttctctg | 1200 |
| ttgtatcccc  | agccccaaag | acagctcctg  | gccatatatc | aaggtttcaa | taaatatttg | 1260 |
| ctaaatgaaa  | aaaaaaaaaa | aaaaaaactc  | ga         |            |            | 1292 |

&lt;210&gt; 190

&lt;211&gt; 906

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (144)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (145)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 190

|            |            |             |             |            |             |     |
|------------|------------|-------------|-------------|------------|-------------|-----|
| actccctcac | ccaggctcca | gccctgggaa  | ccacctaccg  | tgagcccttt | tgagatatata | 60  |
| gactcatttc | atcctcagat | ggtccttcaa  | ggtagggtact | ttagtcccat | tttagagatg  | 120 |
| agacgattga | ggccagaggg | gtgnngtaac  | ttgcctgggg  | gctcacgagc | acaaaaggag  | 180 |
| ccgaggcagg | atctgaccct | tgttctctgg  | cctcactgcc  | ctcactttgc | catgaccoga  | 240 |
| agttatgtcc | ctacaaagca | atgcatggtc  | caaggytctt  | tttattgtat | ttttattttt  | 300 |
| aagggtcctg | ttcaaaactg | gtgtgagctc  | tgaggagtcc  | tgaacctctg | gtgcagcatc  | 360 |
| ctagcatcct | gggagtcctt | ttctgcccac  | actgagctgg  | gctcctcgag | gggtggggct  | 420 |
| gctgtccctg | gaagcctggc | agcagcactg  | tatcgggttg  | gctgaagctg | arcgccgtgg  | 480 |
| ggtgcagggc | tccmgaatc  | cccgtttggc  | tgaaggggtt  | ccctgtagcc | mgggatgttt  | 540 |
| atgaggtctc | tctgatgccc | caggcgcagg  | acatgtgtgc  | gggtggagaa | aagcaggccc  | 600 |
| tttcagtgcc | agctccactc | aattttctatg | tggaccaaga  | acgataaact | taaaaaattt  | 660 |
| tttttcttaa | ggtatcttca | gaatatgggtg | tattttttatg | tggaaaagaa | aagttatgaa  | 720 |
| ggcagctggt | actttaagag | aaaattcatt  | aaaagtcctc  | gaggtatgaa | gatgacggcg  | 780 |
| tgcttctcaa | tcattttggc | ataacttgat  | tgtggctgta  | attttttttt | ttttttttgt  | 840 |
| caagcatgtc | agacaataaa | gtctttgtaa  | aaagrgaaaa  | aaaaaaaaaa | aaaaaaaaaa  | 900 |



actcga

906

<210> 191  
<211> 1941  
<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (561)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1414)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1422)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1427)  
<223> n equals a,t,g, or c

<400> 191  
cttcagctga agcccaggga ccccttttcc accctgggccc ccaatgccgt cctttcccccg 60  
cagagactgg tcttggaac cctcagcaaa ctcagcatcc aggacaacaa tgtggacctg 120  
attctggcca cacccccctt cagccgcctg gagaagttgt atagcactat ggtgcgcttc 180  
ctcagtgacc gaaagaaccc ggtgtgccgg agatggctgt ggtactgctg gccaacctgg 240  
ctcaggggga cagcctggca gctcgtgccca ttgcagtga gaagggcagt atcggaacc 300  
tcctgggctt cctagaggac agccttgccg ccacacagtt ccagcagagc caggccagcc 360  
tcctccacat gcagaaccca ccctttgagc caaytagtgt ggacatgatg cggcgggctg 420  
cccgcgcgct gcttgccctg gccaaagggtg acgagaacca ctcagagttt actctgtacg 480  
aatcacggct gttggacatc tcggtatcac cgttgatgaa ctcaktgggt tcacaagtca 540  
tttgtgatgt actgtttttg nattggccag tcatgacagc cgtgggacac ctccccccc 600  
cgtgtgtgtg tgctgtgtgt gagaacttag aaactgactg ttgcccttta tttatgcaaa 660  
accacctcag aatccagttt accctgtgct gtccagcttc tcccttggga aaaagtctct 720  
cctgtttctc tctcctcctt ccacctcccc tccctccatc acctcacgcc tttctgttcc 780  
ttgtcctcac ctactcccc tcaggaccct accccaccct ctttgaaaag acaaagctct 840  
gcctacatag aagacttttt ttattttaac caaagttact gttgtttaca gtgagtttgg 900  
ggaaaaaaaa taaaataaaa atggctttcc cagtccttgc atcaacggga tgccacattt 960  
cataactgtt tttaatggta aaaaaaaaaa aaaaaatac aaaaaaaat tctgaaggac 1020  
aaaaaagggt actgctgaac tgtgtgtggt ttattgttgt acattcaca tcttgaggga 1080  
gccaagaagt tcgcagtgtg gaacagaccc tgttcactgg agaggcctgt gcagtagagt 1140  
gtagaccctt tcatgtactg tactgtacac ctgatactgt aaacatactg taataataat 1200  
gtctcacatg gaaacagaaa acgctgggtc agcagcaagc tgtagttttt aaaaatgttt 1260  
ttagttaaac gttgaggaga aaaaaaaaaa aggcctttcc ccaaagtat catgtgtgaa 1320  
cctacaacac cctgacctct ttctctctc cttgattgta tgaataaccc tgagatcacc 1380  
tcttagaact ggttttaacc tttagctgca gcgctacgt cnawcgntgt gtatatatat 1440  
gacgtkgtag attgcacata cccttggatc cccacagttk ggtcctcctc ccagctaccc 1500  
ctttatagta tgacgagtta acaagttggt gacctgcaca aagcgagaca cagctattta 1560  
atctcttgcc cagatatcgc ccctcttggt gcgatgctgt acaggtctct gtaaaaagtc 1620  
cttgctgtct cagcagccaa tcaacttata gtttattttt ttctggggtt ttgttttgtt 1680  
ttgttttctt tctaactcag gtgtgaaaaa gttctaggtt cagttgaagt tctgatgaag 1740

124

|   |      |
|---|------|
| aaacacaatt gagatTTTTT cagtataaa atctgcatat ttgtatttca acaatgtagc  | 1800 |
| taaaacttga tgtaaattcc tcctTTTTT cctTTTTTgg cttaaatgaat atcatttatt | 1860 |
| cagtatgaaa tctttatact atatgttcca cgtgttaaga ataaatgtac attaaatctt | 1920 |
| ggtaagactt taaaaaaaaa a   | 1941 |

<210> 192  
 <211> 2118  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (13)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1324)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1643)  
 <223> n equals a,t,g, or c

<400> 192

|  |      |
|--|------|
| aaataataat aanaataaat aaaaatwaag tgcttaktgt aactcagcgg acagggctcc  | 60   |
| cagctgctct ggcacgtggg acaccytcca ccotgcacac aacaggcatg caaagaggac  | 120  |
| tggatatggg ggggtagagt gcttctggtg tgttcacttt aagaaaacat ctgccaagag  | 180  |
| agaagagtgc ccaggaaaga ccaggaaaat acaagtacat ggctgcttca taccatatac  | 240  |
| cccaattctt taaagcagca aaaggcactt tttttttcag gccagagtga atctaaaaca  | 300  |
| aacctggctt tgcttacagg gaagctgtcc cagaaggact gagtgatgcc tcttgttccc  | 360  |
| taaggtctgg agagtctttg caagtttcca acgacatttc caaccagggtg ggagagacca | 420  |
| gcagttgacg agacaagtca gacccaaaaa acgacgcca ggtagttagt ggggtgcctat  | 480  |
| ttgggagttag gatgatttga ggaaaacagg aagaaaaacc ggtcagaaag tggcactttg | 540  |
| gaagtggaaa gctgtttgca aatagcaact ctggctaaag cgaaaatgtt aatcaagtag  | 600  |
| aaagtaaaat tcaggatctt agaagctcat ccttctgatg agaactattt ttttttccgt  | 660  |
| gaaggaaacta ttattacttt aaaagttagg gtaatttaca tatgggggtg atatattcta | 720  |
| aaaatagtaa taaaagtacc ttttataagc aatgttgtgt ggcttgtaga agaaagcagg  | 780  |
| gaggaaaaaa aggcaggcaa aactagtcta ggtctaggcc ctaaaaatga gcttccttcc  | 840  |
| cacttgactg gaaacgcccc tgtgatttct aggtcgaaaa taggtaggat ttaacgagta  | 900  |
| acctagtctc cttctgtctc tgatttctga tcagctgatg gagctgctag taagaggggc  | 960  |
| cgatcatgct cccagacgag tcctttggcc tcttgctctc catcccaagc ctgactcctt  | 1020 |
| cagcagcagc cccctccttc tgtgtccatc tgatgcaggc aagcaggagc agtaagaggg  | 1080 |
| catcccatgt tccagttcac cttctatggg gtgactarga ggttcccggg aactagggca  | 1140 |
| gcccargccc agcaggttgc aaaagcagct gcaagcttca gaaacccact tcctccaaca  | 1200 |
| ccaggagggt ggcagagagc ccatccaaaa gccactggg agaggcataa gattctgtgc   | 1260 |
| caggccccca ggtccctctc gtgtcaggta ggtctgtcta ctggcctctg aagtaaaaggc | 1320 |
| aaanacaaac gggcagggca ggggtggcagg aataaaaaac tctggacaga aaccctttta | 1380 |
| ataaaggaaa ttccaccctc cccaatcctt ccatggaagg gtgagacctt aatgtgatgt  | 1440 |
| aagaggaagg tcttctctgg ctttcaggga aacagctgca gctgaaactt aggggccccat | 1500 |
| tccagggcac ttttcaccac agccagtgca gccgtcccaa gtgccactgt cagccccatc  | 1560 |
| actgcccaatt tcacaaagcg gttggtcctt ggcttggtca ggacatcttt tgttcgatct | 1620 |
| tcaggccgca gaagtccccg aanaccgctg ccgcagcacc atatcaggcc tctgtctgggc | 1680 |
| tgatgccagc tcaaagtctt tgaaagtaga ggctgcccgt ctctcagctt gctgttgggc  | 1740 |
| agcggcctcc cgagcaagtt cggatggggg aaactgaaca aaaaggctct ctstctgtctg | 1800 |
| atcagtgtct catagggcaa gtcctgaggg atctgggaca acaggtgggtg gaccgaggcc | 1860 |

125

|            |            |             |            |             |            |      |
|------------|------------|-------------|------------|-------------|------------|------|
| atgtcacagt | cacagtccag | gacttcctgc  | tgcgataca  | acacaatcac  | ggctgcaaag | 1920 |
| taaatacgga | tcagtgggtg | gcaggccagg  | aagaagtcac | ataaccgcac  | gacgtgcctg | 1980 |
| aagtcagaca | ggacatgccc | aaaccagggtg | atgagccagc | tgagggcaaa  | gatggtcctt | 2040 |
| acctcagcac | tctgcatgaa | gtcatggagc  | tctggattca | cctgggtcaat | gatgggcatc | 2100 |
| agatagttta | atatatgc   |             |            |             |            | 2118 |

<210> 193  
 <211> 1538  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (112)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (147)  
 <223> n equals a,t,g, or c

|             |             |            |             |            |             |      |
|-------------|-------------|------------|-------------|------------|-------------|------|
| <400> 193   |             |            |             |            |             |      |
| ccgggttcgg  | ctctgtgtca  | gcagccgggc | ggcgctcggg  | cgggacatgg | cagcctgtac  | 60   |
| agcccggcgg  | cctggccgtg  | ggcagccgct | ggtgggtccc  | gtcgctgact | gngggccggt  | 120  |
| ggccaaggcc  | gctctgtgcg  | cggccgnagc | tggagccttc  | tcgccagcgt | cgaccacgac  | 180  |
| gacgcggagg  | cacctctcgt  | cccgaaaccg | accagagggc  | aaagtgttgg | agacagttag  | 240  |
| tgtgtttgag  | gtgccaaaac  | agaatggaaa | atatgagacc  | gggcagcttt | tccttcatag  | 300  |
| catTTTTTggc | taccgaggtg  | tcgtcctgtt | tccttggcag  | gccagactgt | rtgaccggga  | 360  |
| tgtggcttct  | gcagctccag  | aaaaagcaga | gaacctgtct  | ggccatggct | ccaaggagggt | 420  |
| gaaaggcaaa  | actcacactt  | actatcaggt | gctgattgat  | gctcgtgact | gccacatat   | 480  |
| atctcagaga  | tctcagacag  | aagctgtgac | cttcttggct  | aaccatgatg | acagtcgggc  | 540  |
| cctctatgcc  | atcccaggct  | tggactatgt | cagccatgaa  | gacatcctcc | cctacacctc  | 600  |
| cactgatcag  | gttcccatcc  | aacatgaact | ctttgaaaga  | tttcttctgt | atgaccagac  | 660  |
| aaaagcacct  | ccttttgtgg  | ctcgggagac | gctaaggggc  | tggcaagaga | agaatcaccc  | 720  |
| ctggctggag  | ctctccgatg  | ttcatcggga | aacaactgag  | aacatacgtg | tcactgtcat  | 780  |
| ccccttctac  | atgggcatga  | gggaagccca | gaattcccac  | gtgtactggg | ggcgctactg  | 840  |
| tatccgtttg  | gagaaccttg  | acagtgatgt | ggtacagctc  | cgggagcggc | actggaggat  | 900  |
| attcagtcct  | tctggcacct  | tggagacagt | gcgaggccga  | gggtagtggt | gcagggaacc  | 960  |
| agtgttatcc  | aaggagcagc  | ctgcgttcca | gtatagcagc  | cacgtctcgc | tgcaggcttc  | 1020 |
| cagtgggcac  | atgtggggca  | cgttccgctt | tgaagacact  | gatggctccc | actttgatgt  | 1080 |
| tcggattcct  | cccttctccc  | tggaaagcaa | taaagatgag  | aagacaccac | cctcaggcct  | 1140 |
| tcactggtag  | gccagctgag  | gccccaaagt | cccaggcttg  | gtcaccggga | agaacaactc  | 1200 |
| tcattcccaca | attgctgcag  | aactcttctc | tccccatcat  | gggccacagt | gggtctctta  | 1260 |
| atttgattgt  | ggggttcttt  | ttgtggggag | gggtgggtata | acttttcttc | agaagaccca  | 1320 |
| tgtgggacac  | ctccaaggct  | ggcctcctca | taagccctgc  | ctacaccatg | ttccagtaaa  | 1380 |
| cctctccacc  | aaggaaactgt | gttcagctgc | cacaggcctg  | gaggagtttc | ctggcctgtc  | 1440 |
| acgtgagggt  | tgatcagtaa  | accagtgcas | gyttggccaa  | aaaaaaaaaa | aaaaaaaaaa  | 1500 |
| aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa | aaactcga    |            |             | 1538 |

<210> 194  
 <211> 1098  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE

&lt;222&gt; (283)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (301)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (349)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (438)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 194

|             |            |             |             |            |            |      |
|-------------|------------|-------------|-------------|------------|------------|------|
| agaccctgtc  | tcaaataata | ataataataa  | taatcttatt  | ttggagaata | aagagaccts | 60   |
| tggatttgag  | gtgccatttg | ggtagaaaga  | aaagacgttt  | acaccgagaa | atagtctgtg | 120  |
| ttgccctgaa  | ggagcagagg | gatgcacgc   | tggagggtgac | ctacagttga | agaagactca | 180  |
| ttatgacaga  | ccttgtcctt | cttccttggtg | gaaagtgttt  | cctctgctgc | tactgctcat | 240  |
| gagactcttc  | cccctccctg | tcccagggaa  | ccaaagggct  | ttntaccac  | accctttctt | 300  |
| ngcccccgc   | ctcccatgtc | tgctgtgcct  | ttgtactcag  | caattcttng | tttgtctcca | 360  |
| ttatcttcca  | gccggataca | gagtgaatag  | ttaaccacac  | ttaggtcaaa | taggatctaa | 420  |
| atthttgttc  | ctgctccngt | gtaaagaggc  | cagtgtttgt  | gtgttgcaag | cagccttgga | 480  |
| atagtaactc  | ttctcatttg | tttgggatct  | ggccamcaag  | ttccagaatg | atacacggat | 540  |
| cagtgcagaa  | gttcacagag | ctctcggacc  | ttagggctgt  | tggagaaggc | ttcagcagca | 600  |
| gaactgatgg  | tkawkgytcg | tgttctccat  | cctcaacttt  | ctttgcttcg | atcatacaca | 660  |
| agaatacatt  | tggaaaggca | aaaaatgaac  | actgttgttc  | attgcagccg | tgthttgtga | 720  |
| cacagatgca  | cagtctgctg | tgaagacctt  | ctctcaagtg  | gsatytgga  | gtccatgcca | 780  |
| gatcatgggtg | cttcagaga  | gactgacagc  | tatcaggggt  | tgtggcactt | agtgaggact | 840  |
| ctcctcccc   | agtgtgtgct | gatgacacat  | acacacctga  | caatagcttg | agtcttctct | 900  |
| gttcctttta  | ctctgtagcc | aacatacaca  | tgatttaaaa  | ccctttctaa | atatctatca | 960  |
| tggttcaccc  | ttgtccaaat | gcagagtcag  | agctatttgt  | acttcattat | tatttccaag | 1020 |
| gcgaatagtt  | ggctttcttt | ttgcaaaaat  | aattaaagtt  | tttgtatgtt | gcaaaaaaaa | 1080 |
| aaaaaaaaaa  | ctacgtag   |             |             |            |            | 1098 |

&lt;210&gt; 195

&lt;211&gt; 1001

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 195

|             |             |             |            |            |            |     |
|-------------|-------------|-------------|------------|------------|------------|-----|
| gaattcggca  | cgagatagct  | tgcattctcat | cccagtaaaa | ccacttattt | ataacatata | 60  |
| aacgtattga  | caaggttgaa  | gagcaagatt  | gttctgaggt | gagatgcaaa | tttcaaaggg | 120 |
| gtgagcacta  | attgtttccag | tgattgttta  | tttattggct | aggacataat | tactctcttt | 180 |
| gaggttacac  | atctgcctcc  | aggttcctgt  | gtgcttgctg | ccttgggatc | aggccagggc | 240 |
| agactgtgat  | cactgagatt  | caaactccca  | gartaatcag | caagagcttt | ctagagacca | 300 |
| aggccaggcc  | tgatccctga  | gggatgcag   | agaaggcttg | gaatctcatt | ctgctatggg | 360 |
| ggctctctct  | tgatcttctt  | ggagtagcaa  | aaacagcaat | gtgggcccac | tggtgtggcc | 420 |
| taaatgatca  | caaaggtaaa  | tgagtaaagg  | gctcagcaga | tgagtaagga | gccttgtcct | 480 |
| gagaaattag  | cactgggctc  | tgcatcaga   | aacatgtgat | aagcattgcc | cattgcacat | 540 |
| tgcttttatt  | gtgtaaggac  | atgaaattcc  | agttttgcag | agctagtgat | gaatacctga | 600 |
| aggggaattgc | agacatatatt | tatttttatt  | ttaattgaca | gatggaattg | tatatattta | 660 |
| tcatgtacat  | aatcatgctt  | taaaatatgt  | acattatgga | atggctaaat | caaactaacc | 720 |

127

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| taggcattat | ctcatataat | tgtcattttt | gtggcgagaa | gactaaaaat | ctaccctttc | 780  |
| agcattttta | aagaatacaa | tgtgttttat | taacaacagt | caccatttgg | tacactagat | 840  |
| ctcttgaact | tcttcctctt | atctaactga | gatcttgtaa | cctttgataa | cagctcccaa | 900  |
| gcccttcccc | aaccactgct | ccaccctggg | taaccaccat | tctattctca | acttcctggg | 960  |
| aatcaccatt | ctagacacag | ggaagactct | ctaccctctg | a          |            | 1001 |

&lt;210&gt; 196

&lt;211&gt; 1458

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 196

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ggcacgagat  | aaactgaaat  | aggctcatgca | aatataaaat  | attattttta  | aattattttgt | 60   |
| cataagaaac  | gatggtggcc  | atattttgct  | ttaataatgg  | aaaaaatgtg  | gttagcattc  | 120  |
| tgtggaaggt  | ggcatcaga   | tagtagacat  | tttctaggat  | ttattttctac | ctgcatatgt  | 180  |
| ggaaatgtgt  | actactttag  | atatttttaa  | tggcagctaa  | ctcagaggca  | tcaaaatgtg  | 240  |
| ctaattggtgt | aatatggcct  | ttgtccttgg  | gttctgtttt  | gtaggccttc  | aatcaagcag  | 300  |
| ggcagggccg  | tacagtgaac  | ttgtccttgg  | ccagacgcca  | gcgtctgccc  | ctgaccccg   | 360  |
| ctccactctc  | tgtgtcctgg  | aggaggagcc  | ccttgatgcc  | taccctgatt  | caccttctgc  | 420  |
| gtgccttgta  | ctgaactggg  | aagagccgtg  | caataacgga  | tctgaaatcc  | ttgcttacac  | 480  |
| cattgatcta  | ggagacacta  | gcattaccgt  | gggcaacacc  | accatgcatg  | ttatgaaaga  | 540  |
| tctccttcca  | gaaaccacct  | accggtgagt  | gcaagggagt  | agaaatctgc  | atcagcacat  | 600  |
| cagcacttgg  | ggatctaagt  | aaacctctcg  | gggaaaaatga | ccaagtggat  | gtcatctccc  | 660  |
| agctgtttct  | aagagcccag  | atgtccagag  | tattgtctca  | ccttgatccc  | tcaggccaga  | 720  |
| agacctgtga  | aaaagccaca  | ctgggtcagg  | gactcactgg  | acggttttgt  | gtccactcta  | 780  |
| acctgcaccg  | tctctacccc  | agagtggact  | caaatcctca  | agtcagtcct  | ctgaacattg  | 840  |
| aagtcagaaa  | ttataaaaagg | gctttggcaa  | tatgttagcc  | caagaatttg  | gcttcttcca  | 900  |
| gaaattgtgc  | cgaccttaac  | agtggcttaa  | atgatggtaa  | aacttttaag  | atttctaaaa  | 960  |
| ggatggcatt  | ggagatacgt  | tgacttttat  | taaacaacct  | atagttggtt  | aatgacttct  | 1020 |
| aaaaaaaaat  | ctggagctca  | gggggttcaac | tgaggggaaca | catgttgaga  | atcattgttt  | 1080 |
| actaattaaa  | tgccaggtaa  | ccgttgaaat  | tatcaaaaac  | atcttccacg  | taccagaaag  | 1140 |
| cactcagagg  | atagttctgt  | tatggagaag  | atgaaatggt  | ttagtagtgt  | aggaactatg  | 1200 |
| gaaaggtgag  | cttagatttg  | gatagtaaaa  | cctcaagacc  | ctatttaaaa  | agtattttat  | 1260 |
| gaatgcagca  | taataaattt  | aattcagtgt  | taaattgcaa  | ggctagtata  | ttgagctgaa  | 1320 |
| tgtgaaaaga  | aactcacatt  | gggagaatgc  | caccttttcc  | ttataagata  | gctttgaaga  | 1380 |
| taccatttta  | gacagatgga  | aattgaatag  | ctttagaaaa  | ggcaaatgtt  | tgatcttggg  | 1440 |
| gaaaaaaaaa  | aaaaaaaaa   |             |             |             |             | 1458 |

&lt;210&gt; 197

&lt;211&gt; 1282

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (675)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1195)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 197

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| gaaaaaaaaa | agtatgaccc | agtagctagg | cacctgtggc | cccgccaa   | gtgacacataa | 60  |
| aattaactgt | cacagtatca | tottagaagt | gaaagaagcc | cctttatcct | gcagtgcgcc  | 120 |

128

|            |              |            |             |            |             |      |
|------------|--------------|------------|-------------|------------|-------------|------|
| tctaccacca | cctactgaca   | aagaacatgg | tgctatctgg  | catgggagaa | atgttcagtt  | 180  |
| tgctatggct | tgtatgtgtc   | ccctcaaatt | caagtgttgc  | caatgtgaca | gcatcaagag  | 240  |
| gtggggctct | taagagatca   | ctaggccatg | agggattctc  | ttaggactgg | gatgaaggcc  | 300  |
| cataataaaa | gaggtttcag   | ggagcatcct | gctagcttgc  | cttctgtatg | tgagaacaca  | 360  |
| gcaagaaagc | cctagtcaac   | aagtgccagc | tccttgatct  | tagacttccc | atcctccaga  | 420  |
| actgtgagaa | atacatttct   | gttccttaca | aattaccag   | tctcctgtat | tctgttatag  | 480  |
| cagcacaaaa | tgaagatacc   | atacctgaac | acctgaacat  | tcttcacaag | gtagtaaattg | 540  |
| cactgcttta | ttctgggtctc  | agtattgtgt | gcttaataag  | gaaatgagaa | aggggtggatc | 600  |
| agggcatagg | atgaacaagt   | tactgctaga | cctctcacia  | tgccactaat | ggataagatt  | 660  |
| gtattttcat | catttcttgt   | ctcttcggaa | gctaaccacca | tgctataata | ggcactaaat  | 720  |
| agatgtctaa | aaacacctta   | agtatttgtc | tagaaatctg  | gtgcattgtc | cagaaagaac  | 780  |
| caaaattcma | aataatttca   | aagggcctaa | agcactaktt  | aatcmaaatt | cattagtttt  | 840  |
| taatggact  | accactctca   | aatttaaaat | gtcatcttac  | gttcctcttc | ctcgcattgg  | 900  |
| atttattgct | aaaacctggg   | aaacacttta | atccytttca  | attccattac | cactgtctct  | 960  |
| gtccagaatt | actcgcagac   | taatagtcac | ctgacttctc  | cccctgcac  | ccgatttgct  | 1020 |
| gtctaattct | ggttacaaat   | aagtaactgc | caaactaatc  | tttctaaaaa | gcaagactga  | 1080 |
| tctcgtcact | cctttgtctca  | acaatgtaaa | agctcccatt  | gtctcccaaa | taaaaccagc  | 1140 |
| tttccactgt | gtatacaata   | catccatgat | ctgtatccag  | catcattttg | tattngctca  | 1200 |
| ctttatacac | caccccccat   | gccacatcaa | attaaattat  | cctgataaat | gcaactgcaa  | 1260 |
| aaaaaaaaaa | aaaaaaaaactc | ga         |             |            |             | 1282 |

&lt;210&gt; 198

&lt;211&gt; 951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 198

|             |             |            |            |            |            |     |
|-------------|-------------|------------|------------|------------|------------|-----|
| atttcggaac  | gaggactgaa  | gtgggagcgg | cggcagggta | gaagacagaa | gggggatcta | 60  |
| tggtgtaact  | aaagaatgtt  | tctgttttgt | taattattgt | gtgtgtgtgg | ttttattgtt | 120 |
| tgcttaagag  | aatcaaaaac  | tgaaaaaat  | gagaatacag | gaaatggctc | ttgtttattt | 180 |
| ttttgctgtg  | tttacagctt  | gttaatgtct | tactgtcttt | gtttcaagag | agattttgtt | 240 |
| actgcccagc  | tcgttttgtg  | tcctgagccc | tatgcccagc | ccaccttata | aatcatgcct | 300 |
| gttttagatgt | ttgattttgt  | tctgttttgt | attgttatct | taaaggtgta | taactctgac | 360 |
| atgccagaca  | tcaaatttaag | ctcaaatata | gctctcgttt | aaatgtttta | acacctaat  | 420 |
| tataattctaa | ttgatcccag  | ccactgatgc | atgtacttta | gctacttctg | ctaaataagc | 480 |
| atattaattt  | tccacatcag  | gccatcagat | cttgagaacc | aacagttatc | tagaattccg | 540 |
| tgtctactaa  | tgtttcacct  | gcatgcagcc | ttcattaatt | ttgtagcaaa | atataaagtg | 600 |
| atcattatgt  | agtttctgga  | ttaaaaaat  | ttgtgtgtga | agttgctttg | taaagtgcac | 660 |
| gtggaattaa  | tgggacagtg  | tgccctttgt | gttagatgtt | agagcaaaag | aaagggtcta | 720 |
| tagtgttagt  | attggagcac  | tttgaagata | gatattttca | gaaaagatgt | aggattttaa | 780 |
| agttaaattt  | taaaattttg  | aaaaagatat | gatggcaatt | ggaaatagtc | acaatgaagt | 840 |
| tcttcatcca  | gtaggtgttt  | aacagtgtta | ttttgccact | ggtaatgtgt | aaactgtgag | 900 |
| tgatttacaa  | taaatgatta  | tgaattcaaa | aaaaaaaaaa | aaaaaactcg | a          | 951 |

&lt;210&gt; 199

&lt;211&gt; 1740

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1310)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1736)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1737)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 199

|            |            |             |             |             |             |      |
|------------|------------|-------------|-------------|-------------|-------------|------|
| ttattataat | aatgatgatg | attccaagga  | aaaaacctac  | agcgaatggt  | ccattttctac | 60   |
| cccgcacgca | gacactctcc | ctaacactga  | taacctgagc  | ccccagcact  | ggacggaaga  | 120  |
| atgctggcgt | ctccgtgtgt | actggttcag  | ggttctggcc  | ccagccttgt  | caggaccccc  | 180  |
| tgggtgccag | agccccacc  | cctcccgcaa  | caagcagctg  | atgccccagt  | gattctctat  | 240  |
| acatttttca | cctcggccaa | tatgtccagg  | aaaactgctt  | acttctcttt  | tcttgccctgg | 300  |
| agccttcatt | gttcaccctt | acgttgcaat  | ataggaatta  | atgctacaaa  | ataaaaagtaa | 360  |
| agcttacctg | aaaagtgcac | agtttggggc  | aatggatatct | acatctccca  | ctgtgggaaa  | 420  |
| accagcaaa  | catcaaaact | ctcaattctc  | ctgttaccra  | atgcagatct  | gaattataag  | 480  |
| atgtttatgt | ttgaccattg | tttcaacaat  | gggattttgt  | tacgaattat  | ccctttaact  | 540  |
| gaaccctca  | gttttactgt | ttacattatt  | aggaaaacag  | ggatatcttt  | tgaatctaaa  | 600  |
| aatttgatgt | acagcatgtg | atTTTTgaag  | tttcatgtta  | aagtcacagt  | ataggtgaaa  | 660  |
| taacgtttgt | catattttga | gacgtatcct  | gcagccatgt  | ttttacgtga  | gtgttttagt  | 720  |
| caaagtacat | ggtagacagt | ctttcacaa   | aaaaggaaaa  | ggattttttt  | tcctccaaat  | 780  |
| gtacatttat | caacctaata | attgattttt  | ttaaaaagag  | atttcgcccc  | agtctggttt  | 840  |
| atgaaagttc | attgccctaa | actgtgctga  | ttgtttttta  | tcaagttata  | aatttccaac  | 900  |
| ctagatcatg | tatctaccaa | ctctcctgca  | ttttccaaaa  | ggcattgagc  | ttaaatatta  | 960  |
| gtctgtgcta | gagtaggtta | tccacttaca  | tgctgcgcta  | aagccatgcc  | tttgaaactc  | 1020 |
| cttgttttaa | acatgatatg | atTTTTgtgg  | gcagtttcag  | aaaagaaaac  | aaacaaaaca  | 1080 |
| aaatcgaccc | tttaattatt | acttgcaact  | caacagatct  | ccctgccgta  | ctgccttttc  | 1140 |
| caggaacttt | acttcagggc | tgtccagatt  | gcagttgtgc  | cccgtgtatg  | tggatctagt  | 1200 |
| tcacagagtc | tttggaagcc | agcagtcgtg  | ccctccgtat  | actgtccact  | cattttatgt  | 1260 |
| agatttggtg | tcctcagcag | ccagtgttaa  | caccactgtc  | acgtagttaa  | cagattcatc  | 1320 |
| ttttatgtat | ttaaagtaat | ccatactatg  | atttggtttt  | tccttgcaac  | attaattctg  | 1380 |
| gcacagatc  | agtttttgtg | ttgtgaagtt  | ctactgtggg  | ttgaccaag   | accacaacca  | 1440 |
| tgagaccctg | aagtaaagat | aaggtaacac  | tacattattt  | gagtaactgt  | ttccttgggg  | 1500 |
| gccaatctgt | gtatgctttt | agaagtttac  | agaatgcttt  | tatttttgtc  | tataacaaac  | 1560 |
| agtctgtcat | ttatttctgt | tgataaacca  | tttggaacaga | gtgaggacgt  | ttgccctgtt  | 1620 |
| atctcctagt | gctaacaata | cactccagtc  | atgagccggg  | ctttacaaat  | aaagcacttt  | 1680 |
| tgatgactca | maaaaaaaaa | aaaaaaaaamc | ycggggggggg | gccggttaacc | catttnmccc  | 1740 |

&lt;210&gt; 200

&lt;211&gt; 1707

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 200

|             |             |            |            |             |             |     |
|-------------|-------------|------------|------------|-------------|-------------|-----|
| gcttatagaa  | gggagaggag  | cgaacatggc | agcgcgttgg | cggttttggt  | gtgtctctgt  | 60  |
| gaccatgggtg | gtggcgctgc  | tcacgttttg | cgacgttccc | tcagcctctg  | cccaaagaaa  | 120 |
| gaaggagatg  | gtgttatctg  | aaaaggttag | tcagctgatg | gaatggacta  | acaaaagacc  | 180 |
| tgtaataaga  | atgaatggag  | acaagttccg | tcgccttgtg | aaagcccccac | cgagaaatta  | 240 |
| ctccgttatc  | gtcatgttca  | ctgctctoca | actgcataga | cagtggtgtc  | tttgcaagca  | 300 |
| agctgatgaa  | gaattccaga  | tcctggcaaa | ctcctggcga | tactccagtg  | cattcaccaa  | 360 |
| caggatattt  | tttgccatgg  | tggtttttga | tgaaggctct | gatgtatttc  | agatgctaaa  | 420 |
| catgaattca  | gctccaactt  | tcacaaactt | tcctgcaaaa | gggaaaccca  | aacgggggtga | 480 |
| tacatatgag  | ttacaggtgc  | gggttttttc | agctgagcag | attgcccggt  | ggatcgccga  | 540 |
| cagaactgat  | gtcaatatta  | gagtgttagg | acccccaaat | tatgctggtc  | cccttatgtt  | 600 |
| gggattgctt  | ttggctgtta  | ttggtggact | tgtgtatctt | cgaagagtaa  | tatggaattt  | 660 |
| ctctttaata  | aaactgggatg | ggcttttgca | gctttgtgtt | ttgtgcttgc  | tatgacatct  | 720 |

|            |             |            |             |            |            |      |
|------------|-------------|------------|-------------|------------|------------|------|
| ggtcaaagt  | ggaaccatat  | aagaggacca | ccatatgccc  | ataagaatcc | ccacacggga | 780  |
| catgtgaatt | atatccatgg  | aagcagtcaa | gcccagtttg  | tagctgaaac | acacattggt | 840  |
| cttctgttta | atgggtggagt | taccttagga | atgggtgcttt | tatgtgaagc | tgctacctct | 900  |
| gacatggata | ttggaaagcg  | aaagataatg | tgtgtggctg  | gtattggact | tgttgtatta | 960  |
| ttcttcagtt | ggatgctctc  | tatttttaga | tctaaatata  | atggctaccc | atacagcttt | 1020 |
| ctgatgagtt | aaaaaggtcc  | cagagatata | tagacactgg  | agtactggaa | attgaaaaac | 1080 |
| gaaaatcgtg | tgtgtttgaa  | agaagaatg  | caacttgtat  | attttgtatt | acctcttttt | 1140 |
| ttcaagtgat | ttaaatagtt  | aatcatttaa | ccaaagaaga  | tgtgtagtgc | cttaacaagc | 1200 |
| aatcctctgt | caaaatctga  | ggtatttgaa | aataattatc  | ctcttaacct | tctcttccca | 1260 |
| gtgaacttta | tggaaacattt | aatttagtac | aattaagtat  | attataaaaa | ttgtaaaact | 1320 |
| actactttgt | tttagttaga  | acaaagctca | aaactacttt  | agttaacttg | gtcatctgat | 1380 |
| tttatattgc | cttatccaaa  | gatggggaaa | gtaagtctcg  | accaggtggt | cccacatatg | 1440 |
| cctgttacag | ataactacat  | taggaattca | ttcttagctt  | cttcactctt | gtgtggatgt | 1500 |
| gtatacttta | cgcactcttc  | cttttgagta | gagaaattat  | gtgtgtcatg | tggtcttctg | 1560 |
| aaaatggaac | accattcttc  | agagcacacg | tctagccctc  | agcaagacag | ttgtttctcc | 1620 |
| tcctccttgc | atatttccta  | ctgaaataca | gtgctgtcta  | tgattgtttt | tgttttgttg | 1680 |
| tttttyyag  | atcacgytac  | tgggctc    |             |            |            | 1707 |

&lt;210&gt; 201

&lt;211&gt; 779

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 201

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| ctgtccccag | tgtttccagg | taatgacttg | gcactccaga | gaaagtttca | trctgttgcg | 60  |
| tgtggtggct | ccaagccaag | cacctggcat | gcaggtcagc | ccttcccagc | gggcgtggcg | 120 |
| tcgtcctctt | cacagatgcc | acgttgagc  | cccaaggcct | caccattttg | cgttttttag | 180 |
| aaaccatttt | tcttggtcat | ttataaagct | gctttataga | tatctttgat | cctggcatgc | 240 |
| cttggtttcc | tctcccttcc | ctctttccaa | tcttggtttc | ctaacctcct | cttgtagtaa | 300 |
| ttctcaactc | aactcaaat  | cccaagaatt | tggaatggta | ggatgctgtg | cggggagctc | 360 |
| gaggctgagg | cataatcact | gcttcggttc | tgctcatcag | gggacacgct | cccttactca | 420 |
| tggcagccat | gtttgattgt | cacagagccc | cccgaatact | ctgtctatag | tgacacactg | 480 |
| taggtgtcat | aaattttaag | aaacctgctt | ttaagtacta | tttataggtt | tttctgttat | 540 |
| acttgcaacc | tagttttaaa | atacatgagg | attttatgaa | agctttatag | agacatttat | 600 |
| aggaaactca | ttctttgatt | ttaggtgcca | tttaaattga | taacacttac | tttataaaaa | 660 |
| gatgcttttt | gtctggatag | agccttatag | tttaaaatat | cttcatatat | tgccatttga | 720 |
| tcaaataaat | ttcttactta | gaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaactcga  | 779 |

&lt;210&gt; 202

&lt;211&gt; 1617

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 202

|            |             |            |             |             |             |     |
|------------|-------------|------------|-------------|-------------|-------------|-----|
| ggcacagctt | tctgtctctt  | cctcgctccc | tctctttctc  | tcctccctct  | gccttcccag  | 60  |
| tgcataaagt | ctctgtcgct  | cccggaactt | gttggcaatg  | cctatttttt  | ggctttcccc  | 120 |
| cgcgttctct | aaactaaacta | tttaaaggct | tgcggtcgca  | aatggtttga  | ctaaacgtag  | 180 |
| gatgggactt | aagttgaacg  | gcagatatat | ttcactgac   | ctcgcggtgc  | aaatagcgta  | 240 |
| tctggtgcag | gccgtgagag  | cagcgggcaa | gtgcgatgcg  | gtcttcaagg  | gcttttcgga  | 300 |
| ctgtttgctc | aagctgggcg  | acacatggcc | aactaccgcg  | agcctgggac  | gacaagacga  | 360 |
| acatcaagac | cgtgtgcaca  | tactgggagg | atttccacag  | ctgcacggtc  | acagccctta  | 420 |
| cggattgcca | ggaaggggcg  | aaagatatgt | gggataaaact | gagaaaaagaa | tccaaaaacc  | 480 |
| tcaacatcca | aggcagctta  | ttcgaactct | gcggcagcgg  | caacggggcg  | gcgggggtccc | 540 |
| tgctcccggc | gttcccggtg  | ctcctgggtg | ctctctcggc  | agcttttagcg | acctggcttt  | 600 |
| ccttctgagc | gtggggccag  | ctccccccgc | gcgccacc    | acactcactc  | catgctccc   | 660 |
| gaaatcgaga | ggaagatcca  | ttagttcttt | ggggacgttg  | tgattctctg  | tgatgctgaa  | 720 |



|             |            |            |            |            |             |      |
|-------------|------------|------------|------------|------------|-------------|------|
| aacactcata  | taggattgtg | ggaaatcctg | attctctttt | ttatttcggt | tgattttcttg | 780  |
| tgtttttatt  | gccaaatggt | accaatcagt | gagcaagcaa | gcacagccaa | aatcggacct  | 840  |
| cagcttttagt | ccgtcttcac | acacaaataa | gaaaacggca | aaccacccc  | attttttaaat | 900  |
| tttattatta  | ttaatttttt | ttgttgga   | aagaatctca | ggaacggccc | tgggcaccta  | 960  |
| ctatattaat  | catgctagta | acatgaaaaa | tgatgggctc | ctcctaatag | gaaggcgagg  | 1020 |
| agaggagaag  | gccaggggaa | tgaattcaag | agagatgtcc | acggacgaaa | catacgggtga | 1080 |
| ataattcacg  | ctcacgtcgt | tcttccacag | tatcttggtt | tgatcatttc | cactgcacat  | 1140 |
| ttctcctcaa  | gaaaagcgaa | aggacagact | gttggctttg | tgtttgagg  | ataggaggga  | 1200 |
| gagagggaag  | gggctgagga | aatctctggg | gtaagagtaa | aggcttccag | aagacatgct  | 1260 |
| gctatggtca  | ctgagggggt | agctttatct | gctgttggtg | atgcatccgt | ccaagttcac  | 1320 |
| tgcttttatt  | ttccctcctc | cctcttggtt | tagctgttac | acacacagta | atacctgaat  | 1380 |
| atccaacggt  | atagatcaca | agggggggat | gttaaatggt | aatctaaaat | atagctaaaa  | 1440 |
| aaagattttg  | acataaaaga | gccttgattt | taaaaaaaaa | agagagagag | atgtaattta  | 1500 |
| aaaagtttat  | tataaattaa | attcagcaaa | aaaagatttg | ctacaaagta | tagagaagta  | 1560 |
| taaaataaaa  | gttattgttt | gaaaaaaaaa | aaaaaaaaaw | ctcgaccgca | aggggaat    | 1617 |

&lt;210&gt; 203

&lt;211&gt; 1974

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 203

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| gaattcggca  | cgaggctgag | ggagctgcag  | cgcagcagag  | tatctgacgg  | cgccagggtg  | 60   |
| cgtaggtgcg  | gcacgaggag | ttttcccgcc  | agcaggagg   | tcctgagcag  | catggcccgg  | 120  |
| aggagcgcc   | tcctgcccgc | cgcgctctgg  | ctctggagca  | tcctcctgtg  | cctgctggca  | 180  |
| ctgcccggcg  | aggccggggc | gccgcaggag  | gagagcctgt  | acctatggat  | cgatgctcac  | 240  |
| caggcaagag  | tactcatagg | atgtgaagaa  | gatatcctga  | ttgtttcaga  | ggggaaaatg  | 300  |
| gcacctttta  | cacatgattt | cagaaaagcg  | caacagagaa  | tgccagctat  | tcctgtcaat  | 360  |
| atccattcca  | tgaattttac | ctggcaagct  | gcagggcagg  | cagaatactt  | ctatgaattc  | 420  |
| ctgtccttgc  | gctccctgga | taaaggcatc  | atggcagatc  | caaccgtcaa  | tgctcctctg  | 480  |
| ctgggaacag  | tgcttcacaa | ggcatcagtt  | gttcaagttg  | gtttcccatg  | tcttggaaaa  | 540  |
| caggatgggg  | tggcagcatt | tgaagtggat  | gtgattgtta  | tgaattctga  | aggcaacacc  | 600  |
| attctccaaa  | cacctcaaaa | tgtatctctc  | tttaaaacat  | gtcaacaagc  | tgagtgccca  | 660  |
| ggcgggtgcc  | gaaatggagg | cttttgtaat  | gaaagacgca  | tctgcgagtg  | tcctgatggg  | 720  |
| ttccacggac  | ctcactgtga | gaaagccctt  | tgtaccccac  | gatgtatgaa  | tggtggactt  | 780  |
| tgtgtgactc  | ctgggttctg | catctgccca  | cctggattct  | atggagtga   | ctgtgacaaa  | 840  |
| gcaaaactgct | caaccacctg | ctttaatgga  | gggacctgtt  | tctaccctgg  | aaaatgtatt  | 900  |
| tsccctccag  | gactagaggg | agagcagtg   | gaaatcagca  | aatgcccaca  | accctgtcga  | 960  |
| aatggaggta  | aatgcattgg | taaaagcaaa  | tgtaagtktt  | ccaaagggtta | ccaggggagac | 1020 |
| ctctgttcaa  | agcctgtctg | cagacctggc  | tgtgggtgcac | atggaacctg  | ccatgaaccc  | 1080 |
| aacaaatgcc  | aatgtcaaga | aggttggcat  | ggaagacact  | gcaataaaag  | gtacgaagcc  | 1140 |
| agcctcatca  | atgccctgag | gccagcaggc  | gcccagctca  | ggcagcacac  | gccttcactt  | 1200 |
| aaaaaggccg  | aggagcggcg | ggatccacct  | gaatccaatt  | acatctggtg  | aactccgaca  | 1260 |
| tctgaaacgt  | tttaagttac | accaagttca  | tagcctttgt  | taacctttca  | tgtgttgaat  | 1320 |
| gttcaataaa  | tgttcattac | acttaagaat  | actggcctga  | attttattag  | cttcattata  | 1380 |
| aatcactgag  | ctgatattta | ctcttccctt  | taagttttct  | aagtacgtct  | gtagcatgat  | 1440 |
| ggtatagatt  | ttcttggttc | agtgtcttgg  | gacagatttt  | atattatgtc  | aattgatcag  | 1500 |
| gttaaaat    | tcagtgtgta | gttggcagat  | attttcaaaa  | ttacaatgca  | tttatgggtg  | 1560 |
| ctgggggcag  | gggaacatca | gaaagggttaa | attgggcaaa  | aatgcgtaag  | tcacaagaat  | 1620 |
| ttggatgggtg | cagttaatgt | tgaagttaca  | gcattttcaga | ttttattgtc  | agatatttag  | 1680 |
| atgtttgtta  | cattttttaa | aattgtctct  | aattttttaa  | ctctcaatac  | aatatatatt  | 1740 |
| gaccttacca  | ttattccaga | gattcagtat  | taaaaaaaaa  | aaaattacac  | tgtggtagtg  | 1800 |
| gcatttaaac  | aatataatat | attctaaaca  | caatgaaata  | gggaatataa  | tgtatgaact  | 1860 |
| ttttgcattg  | gcttgaagca | atataatata  | ttgtaaacaa  | aacacagctc  | ttacctataa  | 1920 |
| aacattttat  | actgtttgta | tgtataaaat  | aaaggtgctg  | ctttagtttt  | ctga        | 1974 |

<210> 204  
 <211> 1057  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (31)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (50)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (132)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (751)  
 <223> n equals a,t,g, or c

<400> 204  
 cggccttccg gggcaaccgt tcgtcccaac ncgggaaagg gtcctggagn cgggaactag 60  
 gagcctcggg agtccaaggg cggagcgccc tttgctaata agccaatcag aacgtgagac 120  
 gctccggtgg gncggtgccg tcgagcgccg ggtggagtct gggtgacttg gctggcggga 180  
 tcaagtgcag ctgcttcagg ctgaggtggc agatagttag cgctgggtggc ggagttaaag 240  
 tyaaagcagg agagtaatawa tgaatagcgc agcgggattc tcacacctag accgtcgcga 300  
 gcgggttctc aagttagggg agagtttcga gaagcagccg cgctgcgctt ccacactgtg 360  
 cgctatgact tcaaacctgc ttctattgac acttcttctg aaggatacct tgagkttggc 420  
 gaagktgaac agktgaccat wactctgccm aatatagaaa gttgaaggaa gcagtaaaat 480  
 tcagtatcgt aaagaacaac agcaacaaca atgtggaatt casccaggac tcccaatctt 540  
 gtaaaacatt ctccatctga agataagatg tccccagcat ctccaataga tgatatcgaa 600  
 agagaactga aggcagaagc tagtctaatt gaccagatga gtagttgtga tagttcatca 660  
 gattccaaaa gttcatcatc ttcaagtagt gaggatagtt ctagtgactc agaagatgaa 720  
 gattgcaaat cctctacttc tgatacaggg naatttgtgtc tcaggacatc ctaccatgac 780  
 acagtacagg attcctgata tagatgccag tcataataga tttcgagaca acagtggcct 840  
 tctgatgaat actttaagaa atgatttgca gctgagtga tcaggaagtg acagtgatga 900  
 ctgaagaaat atttagctat aaataaaaaat ttatacagca tgtataattt attttgatt 960  
 aacaataaaa attcctaaga ctgagggaaa tatgtcttaa cttttgatga taaaagaaat 1020  
 taaatttgat tcagaaaaaa aaaaaaaaaa aactcga 1057

<210> 205  
 <211> 721  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (264)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

&lt;222&gt; (340)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 205

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gaattcggca | cgagtcaccc | ctctccctct | ttcactccct | tactcttact | ctgttttttg | 60  |
| tgctccagac | agacagaccc | tacctctttt | gcttcttttt | tgtttggttg | ttttgagatg | 120 |
| gagtgtcgct | cttggtgccc | aggctggagt | gcagtggcgc | aatctcggt  | caccacaacc | 180 |
| tctgcctccc | gggttcaagc | aattctcctg | cctcagcctc | ccgagaagct | ggggattaca | 240 |
| ggcatgcgcc | accacaccca | gctnaatttt | atatttttag | tagagatggg | gtttctccat | 300 |
| gttggtcagg | ctggcctcaa | actcccaacc | tcaggtgatn | ccgcctgctt | tggcctcccc | 360 |
| aaagtgtcgg | gattacaggc | gtgagccact | gcgccagcc  | tcttttgctc | ctttatactc | 420 |
| attaactcac | gcctgtaatc | cctgttttgg | gaggccaaag | tgagaagggt | gcttgaggcc | 480 |
| aagagtttga | gactagcctg | ggcaacacag | caagatgcca | tctttataat | aaaaataaaa | 540 |
| ataaaaatca | attagctggg | catggtggaa | cgcacctgta | gtcccagcca | attgagaggc | 600 |
| tgaagtggga | ggatcattga | gcccaggagt | tgaggttgca | gtgagccatg | atcatgtcac | 660 |
| tacactcagc | ctgggcaata | gagggacatg | ttgtctctaa | aaaaaaaaaa | aaaaaactcg | 720 |
| a          |            |            |            |            |            | 721 |

&lt;210&gt; 206

&lt;211&gt; 2465

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 206

|            |            |            |             |             |            |      |
|------------|------------|------------|-------------|-------------|------------|------|
| ccaccattta | tccaactgaa | gaggagtta  | aggcagttca  | gaaaattggt  | tctattactg | 60   |
| aacgtgcttt | aaaactcggt | tcagacagtt | tgtctgaaca  | tgagaagaac  | aagaacaaag | 120  |
| aggagatga  | taagaaagag | ggaggtaaag | acagagcttt  | gaaaggagtt  | ttgcgagtgg | 180  |
| gagtattggc | aaaaggatta | cttctccgag | gagatagaaa  | tgtaacacct  | gttttgctgt | 240  |
| gctcagagaa | accttcaaag | acattattaa | gccgtattgc  | agaaaacct   | cccaaacagc | 300  |
| ttgctgttat | aagccctgag | aagtatgaca | taaaatgtgc  | tgtatctgaa  | gcggcaataa | 360  |
| ttttgaatto | atgtgtggaa | cccaaatg   | aagtcactat  | cacactgaca  | tctccaatta | 420  |
| ttcgagaaga | gaacatgagg | gaaggagatg | taacctcggt  | tatggtgaaa  | gaccaccggg | 480  |
| acgtcttgga | caggcaaaaa | tgccctgacg | ctctggctgc  | tctacgccac  | gctaagtggg | 540  |
| tccaggctag | agctaattgg | ctgcagtcct | gtgtgattat  | catacgcat   | cttcgagacc | 600  |
| tctgtcagcg | agttccaact | tggtctgatt | ttccaagctg  | ggctatggag  | ttactagtag | 660  |
| agaaagcaat | cagcagtgct | tctagccctc | agagccctgg  | ggatgcactg  | agaagagttt | 720  |
| ttgaatgcat | ttcttcaggg | attattctta | aaggtagtcc  | tggacttctg  | gatccttggt | 780  |
| aaaaggatcc | ctttgatacc | ttggcaacaa | tgactgacca  | gcagcgtgaa  | gacatcacat | 840  |
| ccagtgcaca | gtttgcattg | agactccttg | cattccgcca  | gatacacaaa  | gttctaggca | 900  |
| tggatccatt | accgcaaatg | agccaacggt | ttaacatcca  | caacaacagg  | aaacgaagaa | 960  |
| gagatagtga | tggagttgat | ggatttgaag | ctgaggggaa  | aaaagacaaa  | aaagattatg | 1020 |
| ataactttta | aaaagtgtct | gtaaatcttc | agtgttaaaa  | aaacagatgc  | ccatttgttg | 1080 |
| gctgtttttc | attcataata | atgtctacat | tgaaaaattt  | atcaagaatt  | taaaggattt | 1140 |
| catggaagaa | ccaagttttt | ctatgatatt | aaaaaatgta  | cagtgttagg  | tattatttga | 1200 |
| atggaaagac | acccaaaaaa | aaaaatgtgc | tccgactagg  | gggaaaacag  | tagttccgat | 1260 |
| tttttcccat | tatttttatt | ttattttctg | gttgccctag  | cttccccccc  | tatttttgtg | 1320 |
| tcttttatta | actagtgc   | tgtcttatta | aatcttcaact | gtattttaatg | caggatgtgt | 1380 |
| gcttcagttg | ctctgtgtat | tttgatattt | taatttagag  | gttttggttg  | ctttttgaca | 1440 |
| ctagtgttaa | gttactttgt | tatagatggg | atcctttacc  | ccttcttaat  | attttacagc | 1500 |
| agtacgtttt | tttgtaacgt | gagactgcag | agtttgtttt  | tctatatgtg  | aaggattaca | 1560 |
| acacaaaaag | ttatcctgcc | attcgagtgc | tcagaactga  | atgtttctgc  | agatcttggt | 1620 |
| gcatttgtct | ctagtgtgat | atataaaggt | gtaattaaga  | cagagtctctg | ttaatcta   | 1680 |
| caagtttgct | gttagttgtg | cattagcagt | ataaaagcta  | atatatacta  | tatgggtctg | 1740 |
| caacagtttt | aaagcctctg | cataattgat | aataaaaatg  | catgacattc  | ttgtttttta | 1800 |
| tagactttta | aaatcataat | tttaggttta | acacgtagat  | ctttgtacag  | ttgacttttt | 1860 |
| gacatagcaa | ggccaaaaat | aactttctga | atattttttt  | cttgtgtata  | agtggaaagg | 1920 |
| gcatttttca | catataagtg | ggctaacc   | tattttcaaa  | agaacttcat  | cattgtacaa | 1980 |

|             |            |            |            |             |            |      |
|-------------|------------|------------|------------|-------------|------------|------|
| ctaacaacag  | taactagccc | ttaattatgg | tgacagttcc | ttattgggtgt | gtgtgagatt | 2040 |
| actctagcaa  | ctattacagt | ataacacaga | tgatcttctc | cacacacccc  | atcacccaga | 2100 |
| taattttacag | ttctgttaac | agtgagggtg | ataaagtatt | actgataaaa  | aattatctaa | 2160 |
| ggaaaaaaac  | agaaaattat | ttggtgtggc | catcttacct | gcttatgtct  | cctacacaaa | 2220 |
| gctaaatatt  | ctagcagtga | tgtaatgaaa | aattacatct | tactgttgat  | atatgtatgc | 2280 |
| tctggtacac  | agatgtcatt | ttgttgtcac | agcactacag | tgaaatacac  | aaaaaatgaa | 2340 |
| attcatataa  | tgacttaaat | gtattatatg | ttagaattga | caacataaac  | tacttttgct | 2400 |
| ttgaaatgat  | gtatgcttca | gtaaaatcat | attcaaattt | aaaaaaaaaa  | aaaaaaaaaa | 2460 |
| ctcga       |            |            |            |             |            | 2465 |

&lt;210&gt; 207

&lt;211&gt; 1480

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 207

|            |             |            |             |             |             |      |
|------------|-------------|------------|-------------|-------------|-------------|------|
| gaattcggca | cgagctcaag  | ctggcaggtg | gtcggggggag | cggccggaga  | ggagctgccg  | 60   |
| ggagttcgtg | ccctgcagga  | catgacacca | gtggcatatc  | acggccatgg  | ggtctcagca  | 120  |
| ttccgctgct | gctcgccctt  | cctcctgcag | gcgaaagcaa  | gaagatgaca  | gggacgggtt  | 180  |
| gctggctgaa | cgagagcagg  | aagaagccat | tgctcagttc  | ccatatgtgg  | aattcacccg  | 240  |
| gagagatagc | atcacctgtc  | tcacgtgcca | ggggacaggc  | tacattccaa  | cagagcaagt  | 300  |
| aaatgagttg | gtggctttga  | tcccacacag | tgatcagaga  | ttgcgccctc  | agcgaactaa  | 360  |
| gcaatatgtc | ctcctgtcca  | tcctgctttg | tctcctggca  | tctggtttgg  | tggttttctt  | 420  |
| cctgtttccg | cattcagtc   | ttgtggatga | tgacggcatc  | aaagtgggtga | aagtcacatt  | 480  |
| taataagcaa | gactcccttg  | taattctcac | catcatggcc  | accctgaaaa  | tcaggaactc  | 540  |
| caacttctac | acgggtggcag | tgaccagcct | gtccagccag  | attcagtaca  | tgaacacagt  | 600  |
| ggtgaatttt | accgggaagg  | ccgagatggg | aggaccgttt  | tcctatgtgt  | acttcttctg  | 660  |
| cacggtacct | gagatcctgg  | tgcacaacat | agtgatcttc  | atgcgaactt  | cagtgaagat  | 720  |
| ttcatacatt | ggcctcatga  | cccagagctc | cttgagaga   | catcactatg  | tggattgtgg  | 780  |
| aggaaattcc | acagctattt  | aacaactgct | attggttctt  | ccacacagcg  | cctgtagaag  | 840  |
| agagcacagc | atatgttccc  | aaggcctgag | ttctggacct  | acccccacgt  | ggtgtaagca  | 900  |
| gaggaggaat | tggttcactt  | aactccagc  | aaacatcctc  | ctgccactta  | ggaggaaaca  | 960  |
| cctccctatg | gtaccattta  | tgtttctcag | aaccagcaga  | atcagtgcct  | agcctgtgcc  | 1020 |
| cagcaaatag | ttggcactca  | ataaagattt | gcagaattta  | atacagatct  | tttcagctgt  | 1080 |
| tcttagggca | ttataaatgg  | aatcataaac | gtggttctag  | gttatcaaac  | catggagtga  | 1140 |
| tgtggagcta | ggattgtgag  | tgacctgcag | gccattatca  | gtgcctcatc  | tgtgcagaag  | 1200 |
| tcgcagcaga | gagggaccat  | ccaaatacct | aagagaaaac  | agacctagtc  | aggatatgaa  | 1260 |
| ttgtttcag  | ctgttcccaa  | aggcctggga | gctttttgaa  | aagaaagaaa  | aaagtgtgtt  | 1320 |
| ggcttttttt | tttttttagaa | agttagaatt | gtttttacca  | agagtctatg  | tggggcttga  | 1380 |
| ttcacccctt | atccattggc  | tggaacatgg | attggggatt  | tgatagaaaa  | ataaacacctg | 1440 |
| cttttgattc | aaaaaaaaaa  | aaaaaawaaa | aaaaactcga  |             |             | 1480 |

&lt;210&gt; 208

&lt;211&gt; 872

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (422)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (847)

&lt;223&gt; n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (856)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (872)  
 <223> n equals a,t,g, or c

<400> 208  
 cagtatttcc ctcagtactg taagcaaaag tggatggtt ttctttcttt atgtctactc 60  
 tgtcctctgt ggccttctgg tgtaccctc tcttcctagc cattcagtct ctctagtcac 120  
 ctccctagta gctagtgtct tctaagtttt tattttaatta gaacaactcc atttccattt 180  
 caaggtagggt caatggggggg aaaagcctca tgatttaaac tgaagttaac aacacagcgt 240  
 ttaaaatgaa aactcatact ccaacttcta aagtataatt gagctgattt gtttccaaaa 300  
 caaagatatg ctgtacctaa aactgctaaa acaaaaatat aaagacaagg actagggtgat 360  
 taagggggaga gaaaaatcat ytcttttcca ggaaaccttt gctaaaataa gcaaaacttg 420  
 antctatgct tcatggaaac tgacacaaag aaaagaaact gatggattgc acaggccttg 480  
 ttatagaaat agatctataa aaagatctgt ccacaggaaa tatacacctt ctctgggttc 540  
 tgaacttcaa tggggatttg tcacctagggt ctccatctat aggaatacct tcacatacct 600  
 atctattcat gcacatattc tgaaaacagg tacatacaaa attacaacaa aggaaaaaaa 660  
 ttctattgaa cacttaaaaa tagaaacagg ccaggcacgg tggctcatgc tgtaatccca 720  
 acaatttggg aggctgaggg tgggtgatca cctgagggtc ggagtgtgag accagcttgg 780  
 ccaacatggt gaaacccgt cactactaaa aatacaaaaa aaattagcct gtgtggtggc 840  
 acactcntac aatccnggct gactcgggaa an 872

<210> 209  
 <211> 1779  
 <212> DNA  
 <213> Homo sapiens

<400> 209  
 aattgccaaag actgcacaaa attacagtgc taatgtatat ggttgacgtt cacataaaga 60  
 caaaagcatc tgttatgaaa tgagtagtaa tattgggtgg ttgatttggt cttagcagac 120  
 ttggcttcat wtgtgtcttg agataaaatg gccagcataa atgctgttta tattcacgtt 180  
 ttcttaggtg tgtgtgtgca ggccacagca gcatgccctt ggtgtagtca gtgccgaaas 240  
 gggctctgtc cttcttgagc ctgcctgcag ggatgggtct cttttaaagc aggttgtgtg 300  
 cagcattcag tacactgaag gtaagctaaa ccatcaacat ctctgggtgt ttaagatgtt 360  
 attttattgg aacaactgac aaatgaggga tgttagcttt gtggcagaat tccctgcatg 420  
 tgtgataact gatcttgttt tattttttgg cattgcaact gtggcatagt tacaatttct 480  
 gtttgktcat cacatttaaa attggragag aacgcgcttg akggatagag cgccttcagk 540  
 gtactgtttc ttattaactt tacttttttt aaatcaactt gctatagact ttatatacat 600  
 tttgttaaat atagttccta gtgacataga aacgatgcgt agttttcatt tactaattac 660  
 aaatgttgag gcctaattct gaaagtcctc atatttaaaag gctagacaac gtaatgaaat 720  
 ttttaactat ttgtatgtca ttttgaaagt gtactgcttt atggtaaaaag tgtttttcat 780  
 ttgttcattg ttttcattat ttgtgatcat gttgtctttc aatacaggca taaaccttcc 840  
 actcttgaac aaagcagctg ctttttaaaa gcggtaattg cttctttacc ttttatttct 900  
 tttgtaaaatg aagcttttct ttaagaatgt gactttaaag tgttgtctat tgcataaaac 960  
 agttgacact cacttattgt aaagtgaaga ttgttctact gcatgtgaag tggaccatgc 1020  
 agattttctgt atgtttctcag tatgcatcac tagataataa agtcttttct gaacaaggca 1080  
 tttgtagcca tttttaaaaag tttttgtctt cagtgtctgg aagtcaggta aaccataaat 1140  
 agttaaaaagc aaccttttct ttttttctct aaagttttta attgaaagta ttattagtta 1200  
 aagatgtaaa cctagccaaa attaccagtt tattaataat taggatccta attatttcaa 1260  
 aaaatcctac aaatattgtc agctttcagt gtagtggatc tattcctgta gggtatgggg 1320  
 tataattcag gatttaacta atgtttctgc tattttctca cttttccttt tgaatgggtgc 1380

136

|            |            |            |             |            |            |      |
|------------|------------|------------|-------------|------------|------------|------|
| gaaagagaaa | aaggaaaacg | gggcacaggc | cattcgacgc  | cttctccaag | gggtctgatt | 1440 |
| tgctgagaca | ccagcttcac | cttcttaaca | aggcacctaa  | ttacaacaag | catgcacatt | 1500 |
| ttggtgcatt | caagaatgga | aaatcagaat | agcagcattg  | attcttctgg | tgcagetcag | 1560 |
| tggaagatga | tgacaaccag | aagacatgag | ctaagggtaa  | gggactgttc | tgaagaacct | 1620 |
| ttccatttag | tgatcaagat | atggaagctg | atttctgaaa  | atgctcagtg | tgtactctaa | 1680 |
| ttatttatgg | taccatttga | attgtaactt | gcatttttagc | agtgcattgt | tctaattgac | 1740 |
| ttactgggaa | actgaataaa | atatgcctct | tattatcaa   |            |            | 1779 |

&lt;210&gt; 210

&lt;211&gt; 2110

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (750)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 210

|            |            |             |             |             |             |      |
|------------|------------|-------------|-------------|-------------|-------------|------|
| gcggccgctg | cagcccggag | ctgagctagc  | cgctccgagcc | gagccgtccg  | agccggggaa  | 60   |
| gccggcgctg | gctgccgctc | gtggcgggcca | gaggagagga  | gaggcagcag  | catggcgagt  | 120  |
| gtcctgtccc | gacgccttgg | aaagcgggtcc | ctcctgggag  | cccgggtgtt  | gggacccagt  | 180  |
| gcctcggagg | ggcctcggct | gccccaccct  | cggagccact  | gctagaaggg  | gccgctcccc  | 240  |
| agcctttcac | cacctctgat | gacaccccct  | gccaggagca  | gccccaggaa  | gtccttaagg  | 300  |
| ctcccagcac | ctcgggcctt | cagcaggtgg  | cctttmagcc  | tgggcagaag  | gtttatgtgt  | 360  |
| ggtacggggg | tcaagagtgc | acaggactgg  | tggwgcagca  | cagctggatg  | gagggtcagg  | 420  |
| tgaccgtctg | gctgctggag | cagaagctgc  | aggtctgctg  | caggggtggag | gaggtgtggc  | 480  |
| tggcagagct | gcagggcccc | tgtccccagg  | caccacccct  | ggagccccga  | gcccaggccc  | 540  |
| tggcctacag | gcccgtctcc | aggaacatcg  | atgtcccaaa  | gaggaagtgc  | gacgcattga  | 600  |
| aatggatgag | atgatggcgg | ccatggtgct  | gacgtccctg  | tcctgcagcc  | ctgttgtaca  | 660  |
| gagtcctccc | gggaccgagg | ccaacttctc  | tgtttcccgt  | gcgccctgcg  | acctatggaa  | 720  |
| ggagagtggg | gacatctcgg | acagcggcan  | cagcactacc  | agcggtcact  | ggagtgggag  | 780  |
| cagtgggtgc | tccaccccct | cgcccccca   | ccccaggcc   | agccccaagt  | atttggggga  | 840  |
| tgcttttggg | tctccccaaa | ctgatcatgg  | ctttgagacc  | gacccctgac  | ctttcctgct  | 900  |
| ggacgaacca | gctccacgaa | aaagaaagaa  | ctctgtgaag  | gtgatgtaca  | agtgcctgtg  | 960  |
| gccaaactgt | ggcaaagtgc | tgcgctccat  | tgtgggcatc  | aaacgacacg  | tcaaagccct  | 1020 |
| ccatctgggg | gacacagtgg | actctgatca  | gttcaagcgg  | gaggaggatt  | tctactacac  | 1080 |
| agaggtgcag | ctgaaggagg | aatctgctgc  | tgtgctgctg  | gctgctgccc  | cagaccccca  | 1140 |
| gtccctggga | ctcccacctc | cgagccagct  | cccaccccca  | gcattgactg  | cctgcctctg  | 1200 |
| tctgctcttc | caccacctct | gcacaaaagc  | cagtcctccg  | gccagaaca   | tcctggcccc  | 1260 |
| gagtcctccc | tgcctcagg  | ggctctcagc  | aagtcagctc  | ctgggtccct  | ctggcacatt  | 1320 |
| caggcagatc | atgcatacca | ggctctgcca  | tccttccaga  | tcccagtctc  | accacacatc  | 1380 |
| tacaccagtg | tcagctgggc | tgtgcccccc  | tccgcccgcct | gctctctmtc  | tccgggtccgg | 1440 |
| agccggctgc | taagcttcag | cgaagcccca  | gcagccagca  | cctgcgatga  | aatctcatct  | 1500 |
| gatcgtcact | tctccacccc | gggcccagag  | tgggtgccag  | aaagcccag   | gggaggctaa  | 1560 |
| gaagtgccgc | aagtgtatgg | catcgagcac  | cgggaccagt  | ggtgcacggc  | ctgccgggtg  | 1620 |
| aagaaggcct | gccagcgctt | tctggactga  | gctgtctctg  | aggttctact  | ctgttctctg  | 1680 |
| cctgcccggc | agccactgac | aagaggccag  | tgtgtcacca  | gccctcagca  | gaaaccgaaa  | 1740 |
| gagaaagaac | ggaaacacgg | agtttgggct  | ctgttggcta  | aggtgtaaca  | cttaagcga   | 1800 |
| ttttctccca | ttgtgcgaac | attttatatt  | ttaaaaaaaa  | gaaacaaaaa  | tatttttccc  | 1860 |
| cctaaaatag | gagagagcca | aaactgacca  | aggctattca  | gcagtgaacc  | agtgacaaa   | 1920 |
| gaattaatta | ccctccggtt | cccacatccc  | cactctctag  | gggattagct  | tgtgcgtgtc  | 1980 |
| aaaagaagga | acagctcggt | ctgcttcctg  | ctgagtcggg  | gaattctttg  | ctttctaaac  | 2040 |
| tcttcagaaa | aggactgtga | gcaagatgaa  | tttacttttc  | ttaaaaaaaa  | aaaaaaaaaa  | 2100 |
| aaaaactcga |            |             |             |             |             | 2110 |

137

<210> 211  
 <211> 938  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (200)  
 <223> n equals a,t,g, or c

<400> 211  
 ggcacaggaa aaaaaagaaa aaagaaaaaa gaaaaaagtt tttgtaccca cagattagca 60  
 ttttcttgat gtttgaaaaa agtttaagct atgtcctaata ttaaaaatga gcacaaacta 120  
 cttaacagat gtctgttccc tcttctctta cttaaattat ctttattttc accatcacct 180  
 cccagtgccg aacacctgan ctctgtgttt tgtgggttga tcctgggttg ccaagttcct 240  
 atttggtcag tccctggcct gtggggcggg ctcaggaagt ggcattgctct tcamragga 300  
 tcgttcatyt ccagtataac cawtttggtta ataattagttg ataattccca gctttttacca 360  
 gatgattttt gacttatttt tctccttttg acctgttcaa agctaacata tctcggtcag 420  
 ttccgagagg gtgggggatt tgagaatgtg aggaggagtg gggttagaat gggtttgcc 480  
 atctgggcaa ggaaagagtt cctagtcgat tgggcacaat gacaaaatga ttccatggat 540  
 agaatcgtcc catgttgctg gaacacctca cgtgttggtga acgccttaaa ttctgccat 600  
 ccttctctg attccccacc tccctgtagt ttccacagga tttatctctc tgtacccccg 660  
 tctccaact ctactctgtc agcctctcct ccattccctta cttcccttct aaattccagg 720  
 agatgacctc actttgcaaa gcaaattgga gccaccaaat tgtagctctc ctcgggtggaa 780  
 actgcatctg tgcctatccc tgcacctctc tgcagaaagc cgcacctca ggccaagatg 840  
 agtgccctggc ccccatggga gactcagaca ctttgacccc ttgtgacttc agcatctccc 900  
 tctttaaaga ttctctccca acattcagtc gtgctcga 938

<210> 212  
 <211> 1551  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (420)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1017)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1408)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1423)  
 <223> n equals a,t,g, or c

<400> 212  
 aggctggact aagcatagag aaccaggaga gaaagaaaga tttaagagac tgagtaatat 60  
 tttttgacag atcatttaag aaactgagta attttttttt tctccaaaag ggcattgggtt 120  
 ttttttttgt tttgtttttt ctctatttgg cactttctag ggattggtct ataaattttt 180

|            |            |            |            |             |            |      |
|------------|------------|------------|------------|-------------|------------|------|
| tgaagatca  | taggataaat | ttctttgtag | caacttccta | ttttagtgtt  | tatgttaggg | 240  |
| garccccarg | tgtccctgct | gatacgccat | tagggccact | tctcagcctc  | tggtacatc  | 300  |
| ataatgcttt | tttttctatc | ttgccaaagt | ttccmgaaaa | ttkakgtttt  | ctaattttaa | 360  |
| aaaaattggt | tgtggagatg | ggatgggacc | tctttataag | ccctgaaaat  | aagtgatttn | 420  |
| ttttaagtgc | tattctgcta | taaacctgat | tctcactttt | ttctgtagac  | aacagttttt | 480  |
| tataatatat | ctattttgtg | tggacattat | ttccttttaa | ccaatactga  | aattccatag | 540  |
| tgtawacttt | ctccacattt | tctttgatta | atacttyctt | aaaatagaca  | cttggattgg | 600  |
| caccagctgt | caccaataaa | gctgccctga | acattgtcaa | tcaatcctgt  | taaccaattt | 660  |
| gagaattttt | ctggaatgct | tagttaggga | tgaatttgct | gggttatagg  | tatgagtatg | 720  |
| cttgatatac | ttttctccag | aatgtctaca | cctgtgtgta | caccacatct  | ccagagatag | 780  |
| gggaatctta | tgtccctgct | aactgctctc | gttatttaat | tttctgacat  | ttgccgccgc | 840  |
| cgccgccccc | tgcccccac  | acacacatgg | tataaagtgg | tagtttcttg  | ttttaaatgg | 900  |
| aacttttgaa | tgatttgaat | ttgggcattt | ctttgtatcc | tgagttattt  | tggtttcccg | 960  |
| ttatgtgaat | atccttttcc | tatgctttaa | ctacttttct | aatttgtccc  | tttttnggt  | 1020 |
| tatcaaattc | caggccattg | tctattccat | cgtcactttt | gggtattgga  | aacatctttc | 1080 |
| cattctgtag | cctgtctgtt | gaacataaat | cttgattttt | atgtaatcag  | atttttctcc | 1140 |
| ttacggttat | gttcttgga  | ttttatttaa | gaaatctttt | tctatcctga  | gaccacaaaa | 1200 |
| atgtccccc  | cattttcttc | tgtttcatag | ttttgccttg | tatgtttaat  | cctttaaggc | 1260 |
| atgtgtagtt | cattttatat | ggtgtgaaat | agttcttatt | catttattca  | acacatatgt | 1320 |
| gtggagtgcc | tgctgatggg | agtactcttc | agagtacttt | gtatatattt  | gtgaacacat | 1380 |
| attcttgccc | tggaagctta | tggtgtcntt | caaggtagat | ccntactcgg  | tttccacctg | 1440 |
| ttttcttcag | ccctcaggat | gaattccaca | attttacaca | tagcaccagt  | taaggaatag | 1500 |
| gctttattgg | agaaaaggaa | ggcttattag | accagcatca | gcaaaaaaaaa | a          | 1551 |

&lt;210&gt; 213

&lt;211&gt; 997

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 213

|             |            |            |            |             |             |     |
|-------------|------------|------------|------------|-------------|-------------|-----|
| agagagtcc   | caacagaacc | taatcatgct | ggcaccctaa | tctcatactt  | ctagcctcca  | 60  |
| gaactgagag  | aacataaact | ccagttgttt | aagctaccca | gtctatggta  | tttgttatta  | 120 |
| tagcccaagc  | taagtcagg  | ggaaaggcag | aaatatattt | agaagartca  | tttctacaaa  | 180 |
| aacagagttg  | ttctaaatga | aatggccaga | tatttcatct | tcttcatact  | agtattttatg | 240 |
| aaagtttcat  | taaaccacc  | ttggccagca | cccaggcctg | ccaccctcag  | aacggcaaac  | 300 |
| aaaagcaaat  | gatttgagga | acaaaagagt | ggacacagag | cctctcagaa  | gatggctcca  | 360 |
| tcttctgaga  | tgatcttctg | agatcatcaa | ttttctgcac | ctgatgtcct  | actccaattg  | 420 |
| tagtagataa  | gagcaaagac | acttcctgat | cctgtggaaa | atgctggagc  | cctgctgatg  | 480 |
| gagaggctga  | cactgggacc | aacagaaggc | cggacattta | tttgcctgcag | cccttctgca  | 540 |
| cctgggccct  | cttcaggcct | tgtaccttgc | actcccatg  | ccactgtagc  | acctggtaag  | 600 |
| ctgaagttag  | gtatttgaag | agataatttg | cccccaacaa | agaattactt  | aaaagaaaaa  | 660 |
| ggaaaccact  | aaattccact | tgacaaacca | gtttgttcag | ttttgacttt  | tgcaaatgtg  | 720 |
| aaactttctc  | tttggcacca | tatgattctg | ttacattagg | gctcatcaat  | gctaagatac  | 780 |
| acagctaggt  | ctaccagctg | ccagtggtca | agaatgaaag | aacctctcag  | agagagatca  | 840 |
| gtttcttaata | acctaacagt | tttccttggs | tattacmaaa | aaaaaaaaaa  | ttagaataaa  | 900 |
| atgtcagtg   | catgcaggca | agtacagata | tggaaatgaa | agctctgtct  | acaactgcaa  | 960 |
| gatttgtttg  | ttaataaaat | tgattgggat | cactcga    |             |             | 997 |

&lt;210&gt; 214

&lt;211&gt; 1496

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (450)



<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (451)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (454)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1485)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1492)

<223> n equals a,t,g, or c

<400> 214

|             |             |            |            |            |             |      |
|-------------|-------------|------------|------------|------------|-------------|------|
| gaattcggca  | cgagtgacca  | cagatatctt | tggtcttcag | cctcaccaca | atgctgtcca  | 60   |
| ctatgttttt  | tttaatcgat  | tgacatctca | tgaatccaca | aatttagccg | cttttccatc  | 120  |
| ttttccatct  | ttgtcatagc  | ttcatcacgc | acgatggagg | tcacttcagc | actatccgga  | 180  |
| gcggcctcac  | ggacagatcr  | gtgaatttcc | ttttcctttt | tcttgatgta | ccggattgtc  | 240  |
| gactcggttaa | cattgagctc  | atggcgaaca | gcactgtaac | tcatgcctga | ttggagctta  | 300  |
| tccaacacgc  | ggamtttctc  | cgtaaggsam | atcamggtct | tctttcgctt | aggaacactg  | 360  |
| ggcararctt  | aarcactacg  | cttggggggc | attttagaaa | gcaaaaccac | ccacaaaaag  | 420  |
| cagaaaaaaa  | agtgtcagta  | aacagactgn | nganaggact | ctttgtttac | agcacaggag  | 480  |
| ctgcgactag  | aaggcggcgc  | ttctccccag | ttcaaaactt | agctgggaac | cttacctccg  | 540  |
| ccaactccaa  | attttcaccc  | tctgcgcagt | cccgggaaas | aaacccccag | aacagtaccg  | 600  |
| tgatgattga  | ttttagggtt  | acaaatacat | tttagcaagt | aagtgaattt | ggcattacga  | 660  |
| attaatgatt  | aatgaaggtc  | acctgtattt | ccatagatat | gtaattttat | ttaagcaggt  | 720  |
| ttattatatt  | aaggcggsga  | ggcagcgccg | aagactacaa | gttccagcat | gcaccgcgtc  | 780  |
| cgggcgggtt  | cgggctccca  | gcgagggctt | cagggaagcc | agcccggagg | catcggccgg  | 840  |
| aagtgtcgta  | gggcaaccac  | gtagtactct | ctgcgcagt  | gcaaagcgct | gtcggggggc  | 900  |
| gccctagctg  | ccgtcgccgc  | cgccggggct | ctatggtctc | tccctagagc | tttgccgttg  | 960  |
| gaggcggctg  | ctgcggtctt  | gtgagtttga | ccagcgctga | gcggcagcaa | catggaggaa  | 1020 |
| ttcgactccg  | aagacttctc  | tacgtcggag | gaggacgagg | actacgtgcc | gtcgggtgag  | 1080 |
| cgattccgcc  | tgaggcgaga  | agcgaattgc | cccgcaccac | gcctcacgtg | agggcgcgctc | 1140 |
| tgcccccgcg  | ggcgtctgcc  | ctgtggccca | ggtggtccag | gggggctcct | gttctcgagc  | 1200 |
| gtccgctccc  | tcaggccccct | catectcggc | cgctccggcc | cgaggcgtgt | gcgcgtggcg  | 1260 |
| gttctgtgct  | ccccctccgt  | tgggcagctc | cgcccgccgc | ccccctcttc | agcgcgggaa  | 1320 |
| cggcacatgg  | acacggcccc  | ttgtcgctag | ggacgctcgt | cggtcagccc | cgaacgacaa  | 1380 |
| cgctgcttca  | gaagtccggg  | cggcagttcg | agccttggaa | gtttttttca | gccctggccc  | 1440 |
| gagagagctg  | ctggccaaca  | acccgtccaa | gatagagctg | tccgntctcc | gnctgg      | 1496 |

<210> 215

<211> 1308

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

140

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1241)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1247)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 215

|            |             |            |             |             |            |      |
|------------|-------------|------------|-------------|-------------|------------|------|
| ttggcancng | ggagaggga   | agaggaggaa | atgggggtttg | aggaccatgg  | cttacctttc | 60   |
| ctgcctttga | cccacacac   | cccatttcct | cctctttccc  | tctccccgct  | gccaaaaaaa | 120  |
| aaaaaaaagg | aaacgtttat  | catgaatcaa | cagggtttca  | gtccttatca  | aagagagatg | 180  |
| tggaaagagc | taaagaaacc  | accctttgtt | cccaactcca  | ctttacccat  | attttatgca | 240  |
| acacaaacac | tgtccttttg  | ggtccttttc | ttacagatgg  | acctcttgag  | aagaattatc | 300  |
| gtattccacg | tttttagccc  | tcaggttacc | aagataaata  | tatgtatata  | taacctttat | 360  |
| tattgctata | tctttgtgga  | taatacattc | aggtgggtgct | gggtgattta  | ttataatctg | 420  |
| aacctaggta | tatccttttg  | tcttcacag  | tcagtgtgag  | gtgggctccc  | tggtatggta | 480  |
| aaaagccagg | tataatgtaa  | cttcacccca | gcctttgtac  | taagctcttg  | atagtggata | 540  |
| tactctttta | agtttagccc  | caatataggg | taatggaaat  | ttcctgccct  | ctgggttccc | 600  |
| catttttact | attaagaaga  | ccagtgataa | tttaataatg  | ccaccaactc  | tggttagttt | 660  |
| aagtgagagt | gtgaactgtg  | tggcaagaga | gcctcacacc  | tcactagggtg | cagagagccc | 720  |
| aggccttatg | ttaaaatcat  | gcacttgaaa | agcaaacctt  | aatctgcaaa  | gacagcagca | 780  |
| agcattatag | ggcatccttg  | aatgatccct | ttgaaatttt  | ttttttgttt  | gtttgtttta | 840  |
| atcaagcctg | aggctgggta  | acagtagcta | cacaccata   | ttgtgtgttc  | tgtgaatget | 900  |
| agctctcttg | aatttgggata | ttggttattt | tttatagagt  | gtaaaccaag  | ttttatattc | 960  |
| tgcaatgcga | acaggtagct  | atctgtttct | aaataaaact  | gtttacattc  | attatggggt | 1020 |
| atgtatgacc | ttcattttcc  | aagaaataga | actctagctt  | agaattatgg  | atgctctaaa | 1080 |
| atgtcagaat | gggaactctc  | ctcgaagttc | tcccaaacctc | agagacagca  | ctgccttctc | 1140 |
| ctaaatgatt | attcttttct  | ccctgttttc | tggtattttc  | taggcacctc  | tctcaccaca | 1200 |
| gccataaccc | ttttttactt  | ccattaggcc | gtataactgg  | ngggacngct  | ggtcggtata | 1260 |
| taatactggg | wccaacamag  | gggttctgga | tgtacacmag  | gttatctt    |            | 1308 |

&lt;210&gt; 216

&lt;211&gt; 1705

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1281)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1704)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 216

141

|             |            |            |             |             |             |      |
|-------------|------------|------------|-------------|-------------|-------------|------|
| tggccatgga  | agcgctagaa | ggtttagatt | ttgaaacagc  | aaagaaggat  | ttccttggat  | 60   |
| ctggagaccc  | caaagaaaca | aagatgctaa | tcaccaaaaca | ggctgactgg  | gccagaaata  | 120  |
| tcaaggagcc  | caaagccgcc | gtggagatgt | acatctcagc  | aggagagcac  | gtcaaggcca  | 180  |
| tcgagatctg  | tggtgaccat | ggctgggttg | acatgttgat  | cgacatcgcc  | cgcaaactgg  | 240  |
| acaaggctga  | gcgcgagccc | ctgctgctgt | gcgctacct   | cctcaagaag  | ctggacagcc  | 300  |
| ctggctatgc  | tgctgagacc | tacctgaaga | tgggtgacct  | caagtccctg  | gtgcagctgc  | 360  |
| agtggagacc  | cagcgctggg | atgaggcctt | tgctttgggt  | gagaagcatc  | ctgagtttaa  | 420  |
| ggatgacatc  | tacatgccgt | atgctcagtg | gctagcagag  | aacgatcgct  | ttgaggaagc  | 480  |
| ccagaaagcg  | ttccacaagg | ctgggcgaca | gagagaagcg  | gtccagggtg  | tggagcagct  | 540  |
| cacaaacaat  | gccgtggcgg | agagcaggtt | taatgatgct  | gcctattatt  | actggatgct  | 600  |
| gtccatgcag  | tgcctcgata | tagctcaaga | tcctgccag   | aaggacacaa  | tgcttggcaa  | 660  |
| gttctaccac  | ttccagcgtt | tggcagagct | gtacctgggt  | tacctgcca   | tccatcgcca  | 720  |
| cacggaagat  | ccgttcagtg | tccatcgctc | tgaaactctt  | ttcaacatct  | ccaggttcct  | 780  |
| gctgcacagc  | ctgcccgaag | acacccctc  | gggcatctct  | aaagtgaata  | tactcttcac  | 840  |
| cttggccaag  | cagagcaagg | ccctcggtgc | ctacaggctg  | gcccggcacg  | cctatgacaa  | 900  |
| gctgcgtggc  | ctgtacatcc | ctgccagatt | ccaaaagtcc  | attgagctgg  | gtaccctgac  | 960  |
| catccgcgcc  | aagcccttcc | acgacagtga | ggagtgtgtg  | cccttgtgct  | accgctgctc  | 1020 |
| caccaacaac  | ccgctgctca | acaacctggg | caacgtctgc  | atcaactgcc  | gccagccctt  | 1080 |
| catcttctcc  | gcctcttctc | acgacgtgct | acacctgggt  | gagttctacc  | tggaggaagg  | 1140 |
| gatcactgat  | gaagaagcca | tctccctcat | cgacctggag  | gtgctgagac  | ccaagcggga  | 1200 |
| tgacagacag  | ctagagattt | gcaaacaaca | gctcccagat  | tcttgctggc  | agtgggagac  | 1260 |
| caagggactc  | catcgagat  | naggacccgt | tcacagctaa  | gctragcttt  | gagcaagggtg | 1320 |
| gctcaragtt  | cgtgccagtg | gtggtgagcc | ggctggtgct  | gcgctccatg  | agccgccggg  | 1380 |
| atgtcctcat  | caagcgatgg | ccccacccc  | tgagggtggc  | atacttccgc  | tactgctgct  | 1440 |
| ctgacgcctc  | cattaccatg | tgcccctcct | gcttcagat   | gttccattct  | gaggactatg  | 1500 |
| agttgctggt  | gcttcagcat | ggctgctgcc | cctactgccg  | cagggtgcaag | gatgaccctg  | 1560 |
| gcccattgacc | agcatcctgg | ggacggcctg | cacctctgc   | cgccttggg   | gtctgctggg  | 1620 |
| ctgtgaagga  | gaataaagag | ttaaactgtc | aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa   | 1680 |
| aaaaaaaaa   | aaaaaaaaa  | aaana      |             |             |             | 1705 |

&lt;210&gt; 217

&lt;211&gt; 999

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 217

|            |            |             |             |            |            |     |
|------------|------------|-------------|-------------|------------|------------|-----|
| agcaaatcac | cttaacgata | tggaaatgaaa | ctgtgaccag  | tgccgccctg | ggtggttctg | 60  |
| gagagactgc | cgtcttcttg | tttggccata  | ggtgctgggg  | ccccggcttc | agtcactgtc | 120 |
| tcagacagka | gtcccataa  | gcagatcacc  | agtcctccac  | tgctcttctc | gtcggccttg | 180 |
| ctgcatgaga | agatagctgc | ttcctccctc  | ttttcttaca  | ctgtaaatta | ttgttttaca | 240 |
| attgagtgyc | ttaataatag | tytacaata   | ctatgtattt  | atgcaaaact | gttaaagtgc | 300 |
| tcactctgta | tgattggata | cttggctctg  | tcagttagtg  | tcagcattgg | gttgtgagct | 360 |
| tgtcctactc | catacgtgtt | tatcctgcta  | tgcatctttac | attgtgtgtt | cacatctatt | 420 |
| ccaaggagcc | ttgctagaaa | caacactggc  | ggttcctgca  | ggccaggcag | gcattggccc | 480 |
| atgctgtgtc | ccataggagc | caatggaaag  | aacgtagctt  | ggtctgctag | ccagccgtgg | 540 |
| ggtggcgcag | gccaggcagc | ctctgcacca  | gagtcagca   | cctgcccatt | ccccagtcac | 600 |
| acaatcatac | tcttctttca | tagagatttt  | attaccacct  | agaccacctt | agttttcttc | 660 |
| tctgttagtg | tcctgagctc | ttttgcaaca  | aaatgtaggt  | acagaccaat | ccctgtccct | 720 |
| tcccataatc | ggagctccac | accatgagtt  | gtttggtttt  | ccagaagctg | ccagtggggt | 780 |
| cccgatgaat | gcgttaagat | atcgatgatk  | ttttttattg  | tttttcttct | tggtttttta | 840 |
| aataatatat | ttaaaggcag | tatcttttgt  | actgtgaatt  | tgcatgtaga | gatgcagaat | 900 |
| gcactttttt | tttacttctg | ttggtgtgta  | ttgtatatag  | tgtgtgtgct | tcttgtgatg | 960 |
| aaaataaact | ttttctttat | aaaaaaaaa   | aaaaaaaac   |            |            | 999 |

&lt;210&gt; 218

&lt;211&gt; 941

142

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 218

|             |             |            |            |            |             |     |
|-------------|-------------|------------|------------|------------|-------------|-----|
| ggcagcagta  | gcatttcatt  | taatctgcag | gtatattctc | ccaacagttt | attgtcatgt  | 60  |
| gatgtcctca  | gccaaagattg | traggcagag | aggagctgtc | ccaacctact | ataccaccga  | 120 |
| ggctggagag  | atcatatttt  | tggtattaaa | ctggagtctc | tccatccttc | acattgttga  | 180 |
| tgctctctgt  | agcaaaccgg  | aaaagtcagt | gacagaagat | gccgctagcg | gtttgagcca  | 240 |
| gagaatgaca  | gctctggttt  | ggagaaaagg | gccggatggg | ggctctagaa | agccccatcct | 300 |
| tctgctcttc  | ttttttctcc  | cccttatatt | gtgctttcat | tcattcattc | attcatcaaa  | 360 |
| catttggtga  | gcacctatta  | tgtgtcaagc | tctgtgctag | cctctggaaa | acctgccctc  | 420 |
| atgtagctca  | ctgtggagta  | ggagaaacaa | tgactacact | atgataagca | cgggttgtca  | 480 |
| gggtctcaca  | gagcagtgcc  | ccctcatcca | gaccgatgag | gtcaaagaag | gcattccaggc | 540 |
| gaggatgggtg | tcagagctaa  | ctgaagaatg | agagggagct | gcaccascag | gggttggaac  | 600 |
| tgaaggtggc  | agtgcctgga  | gtcttgattc | cagcagaggg | agagcagctc | gtgaaaaggc  | 660 |
| accaaggggtg | ggagagggca  | gagcacatgg | aggaacttca | ggtagttctg | gatggcscctg | 720 |
| gggcaaagct  | agagaggtaa  | gaagaatcta | caaattgtcc | tcgagttaca | tgaacttcca  | 780 |
| tcccaataaa  | cccattggaa  | acgaaaaatt | taagtcagaa | gtgcatttaa | ggctgggtccg | 840 |
| agtagaatga  | tttttacaac  | gaattgatca | caaccagtta | cagatgtctt | tgttccttct  | 900 |
| ccactcccac  | tgcttcacct  | gactagcctt | taaaaaaaaa | a          |             | 941 |

&lt;210&gt; 219

&lt;211&gt; 575

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 219

|             |            |             |            |            |            |     |
|-------------|------------|-------------|------------|------------|------------|-----|
| taagtggaaat | ccccgggggt | tgcagggaaat | tcggcacgag | gcattctgag | aagcttaaga | 60  |
| catactttga  | agacaaccct | agggacctcc  | agctgtgcg  | gcatgacctc | cctttgcacc | 120 |
| ccgcagtggt  | gaagccccac | ctgggccatg  | ttcctgacta | cctggttcc  | cctgctctcc | 180 |
| gtggcctgggt | rcgccctcac | aagaagcgga  | agaagctgtc | ttcctcttgt | aggaaggcca | 240 |
| agagagcaaa  | gtcccagaac | ccactgcgca  | gcttcaagca | caaaggaaa  | aaattcagac | 300 |
| ccacagccaa  | gccctcctga | ggttgttggg  | cctctctgga | gctgagcaca | ttgtggagca | 360 |
| caggcttaca  | cccttcgtgg | acaggcgagg  | ctctgggtgt | tactgcacag | cctgaacaga | 420 |
| cagttctggg  | gccggcagtg | ctgggccctt  | tagctccttg | gcacttccaa | gctggcatct | 480 |
| tgccccctga  | caacagaata | aaaatttttag | ctgccccaaa | aaaaaaaaaa | aaaaaaaaaa | 540 |
| ctcgagggggg | ggcccgtacc | caattcgccc  | tataa      |            |            | 575 |

&lt;210&gt; 220

&lt;211&gt; 3018

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 220

|            |             |            |             |            |             |     |
|------------|-------------|------------|-------------|------------|-------------|-----|
| gccagcctta | caggttttac  | gtgaaatgaa | agccattgga  | atagaaccct | cgcttgcaac  | 60  |
| atatcaccat | attattcgcc  | tgtttgatca | acctggagac  | cctttaaaga | gatcatcctt  | 120 |
| catcatttat | gatataatga  | atgaattaat | gggaaagaga  | ttttctccaa | aggaccggga  | 180 |
| tgatgataag | ttttttcagt  | cagccatgag | catatgtcca  | tctctcagag | atctagaact  | 240 |
| tgcctaccaa | gtacatggcc  | ttttaaaaa  | cggagacaac  | tggaaattca | ttggacctga  | 300 |
| tcaacatcgt | aattttctatt | attccaagtt | cttcgatattg | atttgtctaa | tggaaacaaat | 360 |
| tgatgttacc | ttgaagtggg  | atgaggacct | gataccttca  | gcctactttc | cccactocca  | 420 |
| aacaatgata | catcttctcc  | aagcattgga | tgtggccaat  | cggctagaag | tgattcctaa  | 480 |
| aatttgggaa | agatagtaaa  | gaatatgggc | atactttccg  | cagtgacctg | agagaagaga  | 540 |
| tcctgatgct | catggcaagg  | gacaagcacc | caccagagct  | tcaggtggca | tttgctgact  | 600 |
| gtgctgctga | tatcaaactc  | gcgtatgaaa | gccaacccat  | cagacagact | gctcaggatt  | 660 |
| ggccagccac | ctctctcaac  | tgtatagcta | tcctcttttt  | aagggtggg  | agaactcagg  | 720 |

|             |             |             |            |             |             |      |
|-------------|-------------|-------------|------------|-------------|-------------|------|
| aagcctggaa  | aatgttgggg  | cttttcagga  | agcataataa | gattccctaga | agtgagttgc  | 780  |
| tgaatgagct  | tatggacagt  | gcaaaagtgt  | ctaacagccc | ttcccaggcc  | attgaagtag  | 840  |
| tagagctggc  | aagtgccttc  | agcttaccta  | tttgtgaggg | cctcaccag   | agagtaatga  | 900  |
| gtgattttgc  | aatcaaccag  | gaacaaaagg  | aagccctaag | taatctaact  | gcattgacca  | 960  |
| gtgacagtga  | tactgacagc  | agcagtgaca  | gcgacagtga | caccagtga   | ggcaaatgaa  | 1020 |
| agtggagatt  | caggagcagc  | aatgggtctca | ccatagctgc | tggaatcaca  | cctgagaact  | 1080 |
| gagatatacc  | aatatttaac  | attgtttacaa | agaagaaaag | atacagattt  | ggtgaatttg  | 1140 |
| ttactgtgag  | gtacagtcag  | tacacagctg  | acttatgtag | atttaagctg  | ctaatatgct  | 1200 |
| acttaaccat  | ctattaatgc  | accattaaag  | gcttagcatt | taagtagcaa  | cattgcgggt  | 1260 |
| ttcagacaca  | tggtagagtc  | catggctctt  | gtcatcagga | taagcctgca  | cacctagagt  | 1320 |
| gtcggtagag  | tgacctcacg  | atgctgtcct  | cgtgcgattg | ccctctcctg  | ctgctggact  | 1380 |
| tctgcctttg  | ttggcctgat  | gtgctgtctg  | gatgctggtc | cttcatctta  | ggtgttcctg  | 1440 |
| cagttctaac  | acagttgggg  | ttgggtcaat  | agtttcccaa | tttcaggata  | tttcgatgtc  | 1500 |
| agaaataacg  | catcttagga  | atgactaaac  | aagataatgg | cagtttaggc  | tgcaacaactg | 1560 |
| gtaaaatgac  | tgtagataaa  | tggttgaatt  | agtgtacacg | tttgtatttt  | tgtaaatata  | 1620 |
| gccgctgcca  | tagttttcta  | acttgaacag  | ccatgaatgt | ttcatgtctc  | cctttttttt  | 1680 |
| ttgtctatag  | ctgttaccta  | tttttagtgt  | tgaaatgaga | gctagtgatg  | acagaaggat  | 1740 |
| gtggaatgtc  | ttcttgacat  | cattgtgtat  | tgctggtaat | caagttggta  | acgactactt  | 1800 |
| ctagcagctc  | ttaccactat  | gacttaagtg  | gtcctggaag | gcagtaagtg  | gaggtttgca  | 1860 |
| gcattcctgc  | cttcatgagg  | gcttctacca  | ctgaccactt | tgacagtaac  | tggtctccag  | 1920 |
| atttacttag  | gtaccccacg  | agtcgtccac  | ataagcagct | tcatctttac  | cctgccagag  | 1980 |
| ttgacaatta  | tggtgatactc | tagtctactt  | atacttgtgt | tcccatctgt  | ctgccatcct  | 2040 |
| ctgaaggcca  | ggaccacagtc | atacatcctt  | agaaacccaa | gtatgggtttt | tgttttctct  | 2100 |
| tggaaatgtca | ggtccttaag  | catttaattg  | agggacaaaa | aaaaaaaaaa  | gccgatatag  | 2160 |
| tagctagcta  | cttaagcatc  | catgggtatt  | gtcccatatc | aaagcagatt  | tgaggagacag | 2220 |
| aaagagtaaa  | ttagccttca  | gtcttggttt  | acagcttcca | aggagagcct  | tggscacctg  | 2280 |
| aaatgttaac  | tcggctccctt | cctgtctcta  | gttcatcagc | acctgcagat  | gcctgactct  | 2340 |
| tgttagcctt  | actattcaat  | acagtcctta  | gattcacggg | atgcctcttc  | ctatccaggc  | 2400 |
| acctattctg  | aatcaccatg  | ttgctctgca  | gctagagttg | ataggagaaa  | atccatttgg  | 2460 |
| gtagatggcc  | tatgaatttg  | tagtagactt  | tcaaaatgag | tgatttggtta | gcttggtact  | 2520 |
| tttaagtttg  | tggtacagat  | cctccaaacc  | catactctga | gcaattaact  | gccttgaaca  | 2580 |
| tagagaaaaa  | ttaaggcctc  | acaggatgag  | tctccattct | ctgtaaatgc  | ttattttatc  | 2640 |
| atagtcttta  | gcctctaact  | atgagtaaaa  | tgttctcttc | ggccgggtgt  | ggtgactcac  | 2700 |
| acctgtaacc  | tcagcacttt  | gggaggcaga  | ggtgggagga | tcacttaggt  | ccaggagttc  | 2760 |
| gagactagcc  | tgggcaacat  | agtgagacac  | cggatctaca | aaaaaataaa  | aagccagact  | 2820 |
| ggtgggtatgt | atctgtgtcc  | cagctaattg  | ggagggtgag | atgggaggat  | tgtttgagcc  | 2880 |
| taggagaggg  | aggttgcagt  | gagccgtgat  | cgcaccactg | cactccagcc  | tgggcaacag  | 2940 |
| agcaagaccc  | tgtcttggag  | aaaccagaat  | tttggaagag | caaatggggc  | tgagtgcagt  | 3000 |
| ggctcatgcc  | tgtaatcc    |             |            |             |             | 3018 |

&lt;210&gt; 221

&lt;211&gt; 2031

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 221

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| aggatatgca | tgattcttaa | ccaggctata | tgttaaaaaa | aaattggaaa | atgcaataca | 60  |
| ttttttatta | tacaaactac | agaatgagta | tgcaagtttt | atttatcaaa | atgtaatgga | 120 |
| tttttaaagg | ctgagaaatt | ttccttatac | ctaccttttc | agttatttta | attataccaa | 180 |
| attatcaact | agaatagctt | catccatagt | aaatataaaa | tgaagagaca | cctaggctct | 240 |
| atcaggctta | ggattctttg | aacttatttc | cactttaatt | tctcagtggg | agttaagagg | 300 |
| ggtgagaaaa | caaagaaggg | gaaaaactga | caactaacia | aaccagcacc | acatcgctag | 360 |
| gtggtgctta | ctaattacct | tctcaggatt | ttcctcagat | tgaaaagctt | atgaggattt | 420 |
| cttgggagtc | ttaataacct | gcctgttagt | acagagcttt | cctgatgata | tttactcttg | 480 |
| agcacatgtg | gttgtaaaac | cttaactttc | tttctccagg | aggggtggtg | tagaaacaga | 540 |
| tggtagtatt | tatgaactga | tgttctcgtg | aaatgttgag | ggtggggaga | aaagacttta | 600 |
| agggaggaga | gccatctatt | ttgttcctaa | agccacctct | cagcagaatc | gtcatgtttt | 660 |

|            |            |             |             |            |             |      |
|------------|------------|-------------|-------------|------------|-------------|------|
| tctgatgcac | cgctctgctt | catgcccag   | atgacttgcg  | aggcaatctc | aggagctgtg  | 720  |
| gacttaaccr | ttgcaaagca | cactgtcttt  | ctcagcggtc  | tctgcaagtc | agtaggtgtt  | 780  |
| agtatgggtg | caaagttcac | tgtctcagca  | aagttgaact  | gggctacctc | tctacagctg  | 840  |
| tttcctcaga | gggaaaaatc | ttgagaccag  | atgggtggagc | tctggagtc  | gaggaaatgg  | 900  |
| gtgtcttcag | cacaaagctg | ctgcttttac  | ttcagccact  | tctgacattt | ttacataccg  | 960  |
| agcctgagat | trtgtgatta | tctcaaata   | aatcactttg  | atggagataa | ataatcaaaa  | 1020 |
| ctgttttata | gtcattgatt | tggtgagaac  | agtaatggaa  | aatgggtgtg | aaggacttct  | 1080 |
| catttttggg | gcttttcctc | cagagtcctg  | gctgattggt  | gttcgctgtt | catctgagcc  | 1140 |
| cccaaaagca | ttattactga | tacttgacac  | cagtcaaaaag | cgcagactgg | atggatgggtc | 1200 |
| ttttataagg | catttaagg  | tacactactg  | tgtttctactg | accatacatt | tttcttagcc  | 1260 |
| cctcaagtaa | tatagcacag | agttatgaat  | gacaattccc  | ctaaccattc | ctcttcata   | 1320 |
| ctgcctcttc | cccttaccat | cgtaattctc  | caaactgggtc | ataaaggcac | tctgtgaaga  | 1380 |
| tattggggac | tgacatctta | agctctcacc  | tggtctgcagt | aggaaaggcc | aaactgacga  | 1440 |
| caaaaaaaaa | attctttata | aagatgat    | ggtaacatgt  | atctttgccc | tggtctctggg | 1500 |
| tggttccagt | cagtctcaga | tttacaagca  | tttaggagcc  | taggtaaaag | ctgctagtat  | 1560 |
| tcttttaaaa | gttacattta | tgacttgcaa  | tgatagaaaa  | ctccttccaa | ttaaatggca  | 1620 |
| ttttataata | ttatgtgtgt | acttcacagt  | gttaaaaaata | ccctcatagc | ttattgcatt  | 1680 |
| tgatcttcac | agaaagtgc  | ttttaaccag  | tactctgggt  | gcaataaata | atatgtagaa  | 1740 |
| atttaagtcc | tccaattcca | gcataatccag | tgagttttga  | cagtgtgttt | atgtggaatg  | 1800 |
| tttaaggata | tacaattgta | ctttatataa  | attggttctt  | gttcttctta | aatgtgacat  | 1860 |
| gaaataattg | tgctgctaca | ttatactgga  | aattaacagg  | ggaaaaggga | agagctcttg  | 1920 |
| gctcccttga | ggttctgcta | gtgggtgttag | gagtggttac  | aactgagctt | ttagtaacca  | 1980 |
| tttaaccgta | tgtaaacttg | gtttctaatt  | aaaaaaaaat  | ttctttttcc | a           | 2031 |

&lt;210&gt; 222

&lt;211&gt; 968

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (241)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (954)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (961)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 222

|            |             |            |            |             |            |     |
|------------|-------------|------------|------------|-------------|------------|-----|
| ggcacgaggg | ccgcggggaca | tccacggggc | gcgagtgcac | cgcgaggagg  | agagcagtgt | 60  |
| tctgctggag | ccgatgccaa  | aaaccatgca | tttcttatct | agattcattg  | ttttctttta | 120 |
| tctgtggggc | ctttttactg  | ctcagagaca | aaagaaagag | gagagcaccg  | aagaagtga  | 180 |
| aatagaagtt | ttgcatcgtc  | cagaaaactg | ctctaagaca | agcaagaagg  | gagacctact | 240 |
| naaatgccca | ttatgacggc  | tacctggcta | aagacggctc | gaaattctac  | tgacgccgga | 300 |
| cacaaaatga | aggccacccc  | aaatggtttg | ttcttgggtg | tgaggcaagtc | ataaaaggcc | 360 |
| tagacattgc | tatgacagat  | atgtgccctg | gagaaaagcg | aaaagtagtt  | atccccctt  | 420 |
| catttgcata | cggaaaggaa  | ggctatgcag | aaggcaagat | tccaccggat  | gctacattga | 480 |
| tttttgagat | tgaactttat  | gctgtgacca | aaggaccacg | gagcattgag  | acatttaaac | 540 |
| aaatagacat | ggacaatgac  | aggcagctct | ctaaaagccg | gataaacctc  | tacttgcaaa | 600 |
| gggaatttga | aaaagatgag  | aagccacgtg | acaagtcata | tcaggatgca  | gttttagaag | 660 |
| atatttttaa | gaagaatgac  | catgatggtg | atggcttcat | ttctcccaag  | gaatacaatg | 720 |

145

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| tataccaaca | cgatgaacta | tagcatat   | gtatttctac | tttttttttt | tagctattta | 780 |
| ctgtacttta | tgtatwaaac | aaagtcmtt  | ttctccmagt | tgkatttgct | atttttcccc | 840 |
| tatgagaaga | tattttgatc | tccccaatac | attgattttg | gtataataaa | tgtgaggctg | 900 |
| ttttgcaaac | ttaaaaaaaa | atttaaaaaa | actggagggg | ggcccgtacc | caantcgccg | 960 |
| natatgat   |            |            |            |            |            | 968 |

&lt;210&gt; 223

&lt;211&gt; 1404

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1351)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 223

|             |            |             |             |             |            |      |
|-------------|------------|-------------|-------------|-------------|------------|------|
| cgttttccgg  | ccgtgcgttt | gtggccgtcc  | ggcctccctg  | acatgcagcc  | ctctggaccc | 60   |
| cgaggttggg  | ccctactgtg | acacacctac  | catgcggaca  | ctcttcaacc  | tcctctggct | 120  |
| tgccttggcc  | tgcagccctg | ttcacactac  | cctgtcaaag  | tcagatgccg  | aaaaagccgc | 180  |
| ctcaaagacg  | ctgctggaga | agagtcagtt  | ttcagataag  | ccgggtgcaag | accgggggtt | 240  |
| ggtggtgacg  | gacctcaaag | ctgagagtgt  | ggttcttgag  | catcgagctg  | actgctcggc | 300  |
| aaaggcccg   | gacagacact | ttgctgggga  | tgtactgggc  | tatgtcactc  | catggaacag | 360  |
| ccatggctac  | gatgtcacca | aggtctttgg  | gagcaagttc  | acacagatct  | caccctgctg | 420  |
| gctgcagctg  | aagagacgtg | gccgtgagat  | gtttgaggtc  | acgggcctcc  | acgacgtgga | 480  |
| ccaaggggtg  | atgcgagctg | tcaggaagca  | tgccaagggc  | ctgcacatag  | tgccctcggt | 540  |
| cctgttttgag | gactggactt | acgatgattt  | ccggaacgtc  | ttagacagtg  | aggatgagat | 600  |
| agaggagctg  | agcaagaccg | tgggtccaggt | ggcaaagaac  | cagcatttcg  | atggcttcgt | 660  |
| ggtggagggtc | tggaaccagc | tgctaagcca  | gaagcgcgtg  | ggcctcatcc  | acatgctcac | 720  |
| ccacttggcc  | gaggctctgc | accaggcccg  | gctgctggcc  | ctcctgggtc  | tcccgcctgc | 780  |
| catcaccccc  | gggaccgacc | agctgggcat  | gttcacgcac  | aaggagtttg  | agcagctggc | 840  |
| ccccgtgctg  | gatggtttca | gcctcatgac  | ctacgactac  | tctacagcgc  | atcagcctgg | 900  |
| ccctaatagca | ccccgtcctt | gggttcgagc  | ctgcgtccag  | gtcctggacc  | cgaagtccaa | 960  |
| gtggcgaaagc | aaaatcctcc | tggggctcaa  | cttctatggt  | atggactacg  | cgacctccaa | 1020 |
| ggatgcccgt  | gagcctgttg | tcggggccag  | gtacatccag  | acactgaagg  | accacaggcc | 1080 |
| ccgatgggtg  | tgggacagcc | aggyctcaga  | gcacttcttc  | gagtacaaga  | agagccgcag | 1140 |
| tgggaggcac  | gtcgtcttct | acccaaccct  | gaagtccctg  | cagggtcgcc  | tggagctggc | 1200 |
| ccgggagctg  | ggcgttgggg | tctctatctg  | ggagctggcc  | agggcctgga  | ctacttctac | 1260 |
| gacctgctct  | aggtgggcat | tggggcctcc  | gcgggtggacg | tgttcttttc  | taagccatgg | 1320 |
| agtgagtgag  | caggtgtgaa | atacaggcct  | ncactccggt  | tgctgtgaaa  | aaaaaaaaaa | 1380 |
| aaaaaaaaaa  | aaaaaaaaaa | aaaa        |             |             |            | 1404 |

&lt;210&gt; 224

&lt;211&gt; 707

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (705)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (706)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (707)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 224

|             |             |             |            |             |             |     |
|-------------|-------------|-------------|------------|-------------|-------------|-----|
| ngcgcgccctg | cagtcgacac  | tagtggatcc  | aaagaattcg | gcacgagggc  | aggtccaggg  | 60  |
| ctcagaaatc  | agctctattg  | acgaattctg  | ccgcaagttc | cgcttggaact | gcccgcctggc | 120 |
| catggagcgg  | atcaaggagg  | accggcccat  | caccatcaag | gacgacaagg  | gcaacctcaa  | 180 |
| ccgctgcatc  | gcagacgtgg  | tctcgctctt  | catcacggtc | atggacaagc  | tgcgcctgga  | 240 |
| gatccgcgcc  | atggatgaga  | tccagcccca  | cctgcgagag | ctgatggaga  | ccatgcaccg  | 300 |
| catgagccac  | ctcccaccgc  | actttgaggg  | ccgccagacg | gtcagccagt  | ggctgcagac  | 360 |
| cctgagcggc  | atgtcggcgt  | cagatgagct  | ggacgactca | caggtgcgtc  | agatgctgtt  | 420 |
| cgacctggag  | tcagcctaca  | acgccttcaa  | ccgcttcctg | catgcctgag  | cccggggcac  | 480 |
| tagcccttgc  | acagaagggc  | agagtctgag  | gcgatggctc | ctgggtcccct | gtccgccaca  | 540 |
| caggccgtgg  | tcattccacac | aactcactgt  | ctgcagctgc | ctgtctgggt  | tctgtctttg  | 600 |
| gtgtcagaac  | ttttggggccg | ggccccctccc | cacaataaag | atgctctccg  | accttcaaaa  | 660 |
| aaaaaaaaaa  | aaaaactcrg  | gggggggcccc | gtcccaatcc | ccccnnn     |             | 707 |

&lt;210&gt; 225

&lt;211&gt; 1384

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 225

|             |            |            |             |             |             |      |
|-------------|------------|------------|-------------|-------------|-------------|------|
| ggggaaactgc | agtgacagca | ggagtaagag | tgggaggcag  | gacagagctg  | ggacacaggt  | 60   |
| atggagaggg  | ggttcagcga | gcctagagag | ggcagactat  | cagggtgccg  | gcggtgagaa  | 120  |
| tccagggaga  | ggagcggaaa | cagaagaggg | gcagaagacc  | ggggcacttg  | tgggttgag   | 180  |
| agcccctcag  | ccatgttggg | agccaagcca | cactggctac  | cagggtcccct | acacagtccc  | 240  |
| gggctgccct  | tggttctggt | gcttctggcc | ctggggggccg | ggtggggccca | ggaggggtca  | 300  |
| gagcccgtcc  | tgctggaggg | ggagtgcctg | gtggctctgtg | agcctggccg  | agctgctgca  | 360  |
| ggggggcccg  | ggggagcagc | cctgggagag | gcaccccctg  | ggcgagtggc  | atthtctgctg | 420  |
| gtccgaagcc  | amcaccatga | gccagcaggg | gaaaccggca  | atggcaccak  | tggggccatc  | 480  |
| tacttcgacc  | aggtcctggt | gaacgagggc | ggtggctttg  | accgggcctc  | tggctccttc  | 540  |
| gtagcccctg  | tccggggtgt | ctacagcttc | cggttccatg  | tgggtgaagg  | gtacaaccgc  | 600  |
| caaaactgtcc | aggtgagcct | gatgctgaac | acgtggcctg  | tcactctcagc | ctttgccaat  | 660  |
| gatcctgacg  | tgaccgcggg | ggcagccacc | agctctgtgc  | tactgccctt  | ggaccctggg  | 720  |
| gaccgagtgt  | ctctgcgcct | gcgtcggggg | aatctactgg  | gtgggttgga  | atactcaagt  | 780  |
| ttctctggct  | tcctcatctt | ccctctctga | ggacccaagt  | ytttcaagca  | caagaatcca  | 840  |
| gcccctgaca  | actttcttct | gccctctctt | gccccagaaa  | cagcagaggg  | aggagagaga  | 900  |
| ctccctctgg  | ytcttatccc | acytctttgc | atgggammcc  | gtgccaaaaca | cccaagttaa  | 960  |
| agaraarary  | ararctgwgg | caggtatata | gagctggaag  | tggaccatgg  | aaaacatgsa  | 1020 |
| taaccatgca  | tctctctgct | tggccacctc | ctgaaactgt  | ccacctttga  | agtttgaaat  | 1080 |
| ttagtccctc  | camactctga | ctgctgcctc | cttctctcca  | gctctctcac  | tgagttatyt  | 1140 |
| tactgttacc  | tgttccagca | tatccccact | atctctcttt  | ctctgatctc  | gtgctgtctt  | 1200 |
| attctcctcc  | ttaggcttcc | tattacctgg | gattccatga  | ttcatctctt  | cagaccctct  | 1260 |
| cctgccagta  | tgctaaaccc | tcctctctct | tttcttatcc  | cgctgtccca  | ttggcccagc  | 1320 |
| ctggatgaat  | ctatcaataa | aacaactaga | gaatggtggt  | caaaaaaaaaa | aaaaaaaaaac | 1380 |
| tcga        |            |            |             |             |             | 1384 |



147

<210> 226  
 <211> 774  
 <212> DNA  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (773)  
 <223> n equals a,t,g, or c

<400> 226  
 tttaaagatg aagaaatgac aagggagggga gatgagatgg aaagggtgttt ggaagagata 60  
 aggggtctra gaaagaaatt tagggctctg cattctaacc ataggcattc tcgggaccgt 120  
 ccttatccca tttaattaat ttctctgaca attcaattat tttctgttat taatgttgcc 180  
 actgctttct gtttgtctgc actttcttga taaatatttg ctatcgtttt actccagtca 240  
 ttcgatgttg ctgagattta catatgactc ttgtcaacat ctcatctttt gacccaatct 300  
 tattcattta ataagaggtc tcattcattt gcatggaaaa atgctcattg tatattgcaa 360  
 agtgaaaata acgagttgca aaacagtgtg tacatatatg tgtgtatata tgtacacttt 420  
 atttgtacat ttctatgtga cataatgcaa aggaaagtgt ctgattttat tatacaccaa 480  
 aggttaacag tgaatctctg tgtgatctct ttttttttct ttttgctat ctgcactctc 540  
 tcacttgcca aaaaatgaat atatgtttat gtgtgtatat tacttgtgtc acaaaaaacc 600  
 ctaaagtaga cagtaaaaga acttgtcaat cgcctttgga aggcaatgaa acacttaata 660  
 aactctcaat aacagaagcg taaaaatgaa atgtaaacct ccaattacct ctggatctct 720  
 tagccagagt aataaactgg taattattac agataaaaaa aaaaaaaaaa aana 774

<210> 227  
 <211> 865  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (344)  
 <223> n equals a,t,g, or c

<400> 227  
 ccacgcgtcc ggcctttctt ggccagaggg gccggttgga ctcacggggc gggcatgatg 60  
 ggtaacagga ccggtggggg cccaggaag tcctagaggg ggtcgggggt tgggtggaca 120  
 agctttcctc gtccctctcc gacagagctg acgtgtcctg ggttccaccg ggagcgggca 180  
 ttccaccgg acgggagggg tcgggggtgc cggggctggg gaatacgtag gggttgccgc 240  
 gcggtgtggg gagttggggc gtgtggctgc agtcccggga gttcttggag ggggtcggcc 300  
 caccgagctt ccggaccggc tgatctgccc gtagcttgcc gganggargg cggagctgac 360  
 tctccgtccc ttctcccatc ccctccagtg gtgggtacgg gcacctcgct ggcgctctcc 420  
 tccctcctgt ccctgctgct ctttgctggg atgcagatgt acagccgtca gctggcctcc 480  
 accgagtggc tcaccatcca gggcggcctg cttgggtcgg gtctcttcgt gttctcgctc 540  
 actgccttca ataactctga gaactctgtc tttggcaaa gattccaagc aaagatcttc 600  
 cctgagattc tcctgtgcct cctggtggct ctctttgcat ctggcctcat ccaccgagtc 660  
 tgtgtcacca cctgcttcat cttctccatg gttggctgtg actacatcaa caagatctcc 720  
 tccacctgt accaggcagc agctccagtc ctcacaccag ccaaggtcac aggcaagagc 780  
 aagaagagaa actgaccctg aatgttcaat aaagttgatt ctttgtaaaa aaaaaaaaaa 840  
 aaaaaaaaaa aaaaaaaaaa aaaaaa 865

<210> 228  
 <211> 1102  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (462)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (469)  
 <223> n equals a,t,g, or c

<400> 228  
 tttttttttt accattttaaa ataaaatgaa agtgaccttc tgtttataaa aatctttgtc 60  
 tgcattctctg cttatttcct tagaagagat tccaagaagc ggtgagtgat ttcacggcag 120  
 cagaggggttg ggacatatta cgggcgcgga tccctcttgg agtgagatga ctctccggag 180  
 agatttagtc gtcaccctcg cgtgtgaggc tgcgtcacac cccagggatg tgtctatcaa 240  
 gatggaagat cttttacacg ctcttgattt tgtttgscty tttttctatt actagtgaga 300  
 akgaaacttt ttatatgatt attatccatc ataatccaac acaaattact gcttcattgtt 360  
 cttttacttt cctgtgaagg ttttagtgcc ttttaaaaaat tgctatataat taagcttggtt 420  
 aatacttcca tgctgtattt gtggscatca rtttccccgg gnacaggcnt gcacattttg 480  
 ccttcacacg ctgggtggtt tttcattttc amttctattt ctctgtcttc tatcgtttta 540  
 tgttcagacg ggtttctccg tgtagaaagc agtttatgaa gatttacttt cgacagtctt 600  
 ctctctactt tctacagtga attctctgat gtgtctggga gtttgggggt ctgggtaaga 660  
 rtctcctct caccctattc tctattacga tccacagcct catgctttat garattggtg 720  
 gccgggarcg ggggagattt gcggatcccc caagccagac tttatcccc tatccctgcc 780  
 tctggatccc acgtacaggc ctgggaactc cctgtgggta ggggccaatg gtctcgcaact 840  
 ctcacctgta ccccagggct ggcacaggat ggtcaaggag agaggctgcc caagcgcac 900  
 cytctggtgt cccctgaca cgcctccaaa gtgagcaggt aggtttcaac agccccacgt 960  
 tgcaggtggg agatgaagct caggtgggag accagtatct cacagttctc tttgcatggc 1020  
 cgggtacttg ttagtcaact gatcaagtga aaattctagc cccagaggca ggagaatccg 1080  
 gaacaaaatt aaaccagcca gg 1102

<210> 229  
 <211> 744  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (303)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (392)  
 <223> n equals a,t,g, or c

<400> 229  
 gaattcggca cgagagtggc tggagtctgg ctgcagaggg aagacatcag cagggaggga 60  
 gccagggcct gtcacatctt tcctctggcc attgtcctgg tctttgtaag cccagaatct 120  
 ccccttccct gaagggaggg cagcacccca ggagggcagc aggtgtgctg tgaggggttg 180  
 agtagtgtga gaggtcaggg tacactagaa tggccatgga caccatgtgg ggtgctctg 240  
 ggctgggcca cagaacagtg tccttcctgc tgctcctccc ctgcagcttc ccccgacctt 300  
 gtngtttatt tggtttgata ccaatcagca gacctgcaa ggtggaagct cccaggetct 360  
 cagtccacs actctcatgt gccagtcacc cntactgtaa ctgccaatg agtacttctt 420  
 gccactgcc aagatagagc cagtttacca agacagggga attgcagtag agaaagagtt 480  
 gaatatacat agagccagct aaatgggaga gtggagtgtt cttattactt aaatcagct 540

```
<210> 230
<211> 1935
<212> DNA
<213> Homo sapiens
```

```
<220>  
<221> SITE  
<222> (1)  
<223> n equals a,t,g, or c
```

```
<220>  
<221> SITE  
<222> (1921)  
<223> n equals a,t,g, or c
```

```
<220>  
<221> SITE  
<222> (1927)  
<223> n equals a,t,g, or c
```

[illegible]

150

tgaacacgga ggctctctgt tgtctgtctc tgagatcttt gtgtctggga atgcctaaag 1920  
 nttttgnttt ttttt 1935

<210> 231  
 <211> 1035  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1032)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1034)  
 <223> n equals a,t,g, or c

<400> 231  
 agaggcctgg ctgcgttgcc ctatctccgt ctccgccacc cacttagcgt tttaggcatc 60  
 aattaccagc agtttctccg ccactatctg gaaaattacc cgattgctcc cggcagaata 120  
 caagagcttg aagaacgccg cagttgcgtg gaagcctgca gagcaaggga agcagcggtt 180  
 gatgccgaat atcagcgaaa tcctcacagg gtggacctcg atattttaac ctttacgata 240  
 gctctgactg cctctgaagt tatcaaccct ctgatagaag aacttggttg cgataagttt 300  
 atcaatagag aatagttagg tggtagacct acttcaagag aacctctgca ttccagtcac 360  
 accaatcctg caacttgatt ttcagaagtc aagagtatat cgcgataaga cagtgcacag 420  
 gtggagggga aaaaaagggg gagggggaag cttatcttga aaaagcatca cagaagtaga 480  
 aaaaaatgtc gaaagcatta taactgtaac gttctttgag tttgtgattg atccacattt 540  
 ttccccctgc attatggaaa atgtctctca gcattgcttt attacaaagt aaaggatggt 600  
 tttataaaat tgagactgat gaaacatcaa tactagagcc catgaggatg aaagaaatta 660  
 tcaaatagtg ctgaacagaa taagatgtta acgctgagtt attaggactg gaaggctatg 720  
 aaaagaactt gaaattgtcg gaatatgtgc tctcttcatg tcatattcaa tagaagtttc 780  
 tagtttaaga ttgattttgt gttttcttag gcatttcaag tgacaagcaa agtaaatgta 840  
 tatattatgt gataaatcat gttttcaaga acgtcaaat tctggacttt tttctttcaa 900  
 tttttaatth tttaagttht ttttggtatta aaaaatcyat tcacaagcca aaaaatwtwt 960  
 waaatwtwcm gcgaaaagcc aaaaaaaaaa aaammaggg ggggccgggc cccatcccc 1020  
 caaggggggtc cngnt 1035

<210> 232  
 <211> 2218  
 <212> DNA  
 <213> Homo sapiens

<400> 232  
 aggtattagg cccttttgtg ggagcccat gttttgtttt tctgagttgg tggggagggga 60  
 sggaggggga gggctgaatt gttttgcaga ggaagatggc atctgtgctt taaatthtct 120  
 attactgggt tagaaaacaa agagggaktg ccctgcacat tttcttttgt gcttttaaat 180  
 gtttcttaag ttggaacagg tttcctcggg cctgttttga ctgattgctg gagtgcattt 240  
 gatagttaaa aattactaat tggttttatt tcccttcaca ctctgcctcc ccacttctcc 300  
 ccccgttact gaaaaataac ctttttagtg tcaggctaga aattgaattg ctgagttttg 360  
 tgtatccttt aaattaaaaa ccacaagtgt ttattgtagt ggtaaactg tagcatctca 420  
 gcactctggg ggaagctgcc tatatttctt cccagtttaa ctggggacca tctgtgaaat 480  
 taattttcca tccagacagc tgctgtgagc aaatgaacat aaatgctcgc tggaaattht 540  
 ctaaccagtt tttatattga cctgcagtgt aaaaagcaca ttttaattata aacaatatat 600  
 tcaaaatggg caaattttat tttcaaatgc agtgtagagc tagattaaaa gcaactcttt 660  
 gccacctact ctgccctttt ggcaaagtta ccttgaacaa agaattctta gggttttatta 720

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| agaactcttt  | atthttcttca | taccctgttc  | tctgcagtgc  | tttctaacag  | cttctgggtg  | 780  |
| cagatthttct | tggcatcct   | tttgcactca  | gcttattaca  | ggtaggtagt  | gcttaagaaa  | 840  |
| agtcattggag | gactaaagcc  | taagtccttt  | tcactthttcc | tccatctgaa  | ggtaggtagg  | 900  |
| ttcatcctct  | tcatagtaat  | gctgtthttac | caagacttta  | tagcagatgg  | accagaaaa   | 960  |
| aatthttctgc | tattgtgttc  | actacaacag  | gatagggaca  | tcagacagcc  | ccagaaaccc  | 1020 |
| cttcagatc   | tgatatggga  | ctattaatth  | ttatgctgtt  | aattgggtatt | cattcacaat  | 1080 |
| gcagttgaag  | ggggaaggct  | ccactgcatt  | ctttggctaa  | ggcctgaatg  | cttgcctcatc | 1140 |
| tgtaagatct  | atactcgagg  | ttttgtthtc  | ctthtaaaat  | tctthtaggga | gagagggatg  | 1200 |
| gtthctgagg  | ggttctgaaa  | gtatgattca  | atgtgcaaca  | tacaggtagg  | tcttcagcat  | 1260 |
| aagctgaaat  | atatgcatgt  | aaaaacttht  | acatctthtt  | thttaattht  | ccactthctt  | 1320 |
| cttaacttht  | cttctcttht  | tgtccccccc  | ccatcttaca  | gaagttgagg  | ccaagggaga  | 1380 |
| atggtaggca  | cagaagaaac  | atggcaaaact | gctctgtgct  | ttcaaaccaa  | agtgttcccc  | 1440 |
| ccaaccccaa  | atthgtctaa  | gcactggcca  | gtctgttggt  | ggcattgtth  | tctacaacca  | 1500 |
| aattctgggt  | thttthcttc  | thttctthaaa | catagaggta  | ccaccacaag  | ggatgcccta  | 1560 |
| ctctctcgca  | gctcttgaaa  | gcactctgtt  | gagggaaaag  | tctctgggca  | agcaagtggg  | 1620 |
| tatttggtt   | gcttgcctcc  | ctthttccac  | ctgggacatt  | gyaatcataa  | aataacagta  | 1680 |
| aattccaaa   | ctcaaaaact  | attatggcct  | gagcacagct  | gaaatctagc  | agagthtaac  | 1740 |
| tcttctgcct  | ctatgtctgt  | cacttataat  | tcaggttctg  | ctgttggtct  | cagaacatga  | 1800 |
| gcagaagaat  | cgtthttatgc | tagttattgc  | attcatgggt  | gaaactcaac  | ttagggaag   | 1860 |
| ggttccaatg  | tattaagcaa  | tgggctgctt  | ctccccaatc  | ctccccataa  | attcgttggt  | 1920 |
| tggacttctc  | atctaaaagg  | ttagtggctt  | ttgcttggga  | tcagtgtctc  | ctattgatgt  | 1980 |
| tcttctggtt  | ctccagacac  | attcctgttg  | cattaagact  | tgaaagactt  | gtagatgtgt  | 2040 |
| gatgttcagg  | cacaggatgc  | tgaaagctat  | gttactattc  | ttagthttgta | aattgtcctt  | 2100 |
| ttgataccat  | catcttgtth  | tctthttgta  | ggtataaata  | aaaacactgt  | tgacaataaa  | 2160 |
| aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa   | aaaaaaaaa   | 2218 |

&lt;210&gt; 233

&lt;211&gt; 2057

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 233

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ccgagccggc  | tgccgccccg  | gaatccgtgc  | ggcgcccttc  | cgtcccrgtc  | ccatcctcgc  | 60   |
| cgcgctccag  | cacctctgaa  | gtthttgcagc | gccagaaaag  | gagcgaggga  | aggagggagt  | 120  |
| gtgtgagagg  | agggagcaaa  | aagctcaccc  | taaaacattt  | atthcaaggga | gaaaagaaaa  | 180  |
| agggggggcg  | caaaaatggc  | tggggcaatt  | atagaaaaca  | tgagcaccaa  | gaagctgtgc  | 240  |
| atgttggtg   | ggattctgct  | cgtgttccaa  | atcatcgcct  | ttctgggtggg | aggcttgatt  | 300  |
| gtccagggc   | ccacaacggc  | agtgtcctac  | atgtcgggtga | aatgtgtgga  | tgcccgttaag | 360  |
| aaccatcaca  | agacaaaatg  | gttcgtgcct  | tggggaccca  | atcattgtga  | caagatccga  | 420  |
| gacattgaag  | aggcaattcc  | aagggaatth  | gaagccaatg  | acatcgtgtt  | ttctgttcac  | 480  |
| attccctcc   | cccacatgga  | gatgagtcct  | tggttccaat  | tcatgmtgtt  | tatcctgcag  | 540  |
| ctggacattg  | ccttcaagct  | aaacaaccaa  | atcagrgaaa  | atgcagaagt  | ctccatggac  | 600  |
| gtthccctgg  | cttaccgtga  | tgacgcgtth  | gctgagtggga | ctgaaatggc  | ccatgaaaga  | 660  |
| gtaccacgga  | aactcaaatg  | caccttcaca  | tctcccaaga  | ctccagagca  | tggagggccg  | 720  |
| gttactatga  | atgtgatgtc  | cttccthtca  | tggaaattgg  | gtctgtggcc  | catgaagtth  | 780  |
| tacctthttaa | acatccggct  | gcctgtgaat  | gagaagaaga  | aatcaatgt   | gggaattggg  | 840  |
| gagataaagg  | atatccggtt  | ggtggggatc  | cacaaaaatg  | gaggcttcac  | caaggtgtgg  | 900  |
| tttgccatga  | agaccttct   | tacgcccagc  | atcttcatca  | ttatggtgtg  | gtattggagg  | 960  |
| aggatcacca  | tgatgtccc   | acccccagt   | cttctggaaa  | aagtcattct  | tgcccttggg  | 1020 |
| atthccatga  | cctthtatcaa | tatcccagtg  | gaatgggtth  | ccatcgggtt  | tgactggacc  | 1080 |
| tggatgctgc  | tgthttggtga | catccgacag  | gcactthtca  | tgcrtatgctt | ctktccttct  | 1140 |
| ggatcatctt  | ctgtggcgag  | cacatgatgg  | atcagcacga  | gcggaaccac  | atcgcagggt  | 1200 |
| attggaagca  | agtcggaccc  | attgccgttg  | gtccttctgc  | ctcttcata   | ttgacatgtg  | 1260 |
| tgagagaggg  | gtacaactca  | cgaatccctt  | ctacagtatc  | tggactacag  | acattgggaa  | 1320 |
| cagagctggc  | catggcttht  | atcatcgtgg  | ctggaatctg  | cctctgcctc  | taacttctct  | 1380 |
| thttctatgct | tcatggtatt  | tcagggtgtt  | cggaaacatca | gtgggaagca  | gtccagcctg  | 1440 |
| ccagctatga  | gcaaagtcgg  | gcggctacac  | tatgaggggc  | taattthtag  | gttcaagttc  | 1500 |

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| ctcatgctta | tcaccttggc | ctgcgctgcc | atgactgtca | tcttcttcat | cgttagtcag | 1560 |
| gtaacggaag | gccattggga | aatggggcgg | cgtcacagtc | ccaagtgaac | agtgcctttt | 1620 |
| tcacaggcat | ctatgggatg | tggaatctgt | atgtctttgc | tctgatgttc | ttgtatgcac | 1680 |
| catcccataa | aaactatgga | gaagaccagt | ccaatggaat | gcaactccca | tgtaaatega | 1740 |
| gggaagattg | tgctttgttt | gtttcggaac | tttatcaaga | attgttcagc | gcttcgaaat | 1800 |
| attccttcat | caatgacaac | gcagcttctg | gtatttgagt | caacaaggca | acacatgttt | 1860 |
| atcagctttg | catttgagc  | tgtcacagtc | acattgattg | tacttgata  | cgcacacaaa | 1920 |
| tacactcatt | tagcctttat | ctcaaaatgt | taaatataag | gaaaaaagcg | tcaacaataa | 1980 |
| atattctttg | agtattgtct | tacttctctt | aaaaaaaaa  | aaaaaaactc | gtgccgaatt | 2040 |
| cggcacgagc | ggcacga    |            |            |            |            | 2057 |

&lt;210&gt; 234

&lt;211&gt; 2084

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (775)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2080)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2083)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 234

|            |            |            |            |            |             |      |
|------------|------------|------------|------------|------------|-------------|------|
| ggcagagggc | catttcctgc | aaagagccaa | accccatc   | ctctgtgcc  | ctcctctccc  | 60   |
| accaagtgt  | ttataaaaa  | agctcttgt  | accggaaata | actgttcatt | tttcaactc   | 120  |
| cctccttagg | tcacactttt | cagaaaaaga | atctgcatcc | tggaaccag  | aagaaaaata  | 180  |
| tgagacgggg | aatcatcg   | tgatgtgtg  | stgcctttg  | gctgagtgtg | tgagagctc   | 240  |
| ctcaggtgt  | aggtacagt  | tggttgatc  | tggtggctt  | aggggaacc  | cttgttcaga  | 300  |
| gctgtgactg | cggctgcact | gcagagaagc | tgcccttgg  | tgctcgtagc | gccgggcctt  | 360  |
| ctctcctcgt | catcatccag | agcagccagt | gtccgggagg | cagaaggtag | cggggcagct  | 420  |
| actggaggac | tgtgcggggc | tgccctgggt | gccccctcc  | ccgtggggcc | ctgttgctgc  | 480  |
| tgtccatcta | tttctactac | tcctcccaa  | atgcggtcgg | cccgccttc  | acttgatgc   | 540  |
| ttgccctcct | gggccttctc | gcaggcactg | aacatcctcc | tgggcctcaa | gggcctggcc  | 600  |
| ccagctgaga | tctctgcagt | gtgtgaaaa  | gggaatttca | acgtggccca | tgggctggca  | 660  |
| tggtcatatt | acatcgga   | tctgcggctg | atcctgccag | agctccaggc | ccggattoga  | 720  |
| acttacaatc | agcattacaa | caacctgcta | cggggtgcag | tgagccagcg | gtgtnatatt  | 780  |
| ctcctcccat | tggaactgtg | ggtgcctgat | aacctgagta | tggtgaccc  | caacattcgc  | 840  |
| ttcctggata | aactgcccc  | gcagaccggg | gaccgtgctg | gcatcaagga | tcgggtttac  | 900  |
| agcaacagca | tctatgagct | tctggagaac | gggcagcggg | cgggcacctg | tgctcctggag | 960  |
| tacgccaccc | ccttgacagc | ttgttttggc | atgtcacaat | acagtcaagc | tggtcttagc  | 1020 |
| ggggaggata | ggcttgagca | ggccaaactc | ttctgcggga | cacttgagga | catcctggca  | 1080 |
| gatgcccctg | agtctcagaa | caactgccgc | ctcattgcct | accaggaacc | tcagatgac   | 1140 |
| agcagcttct | cgtgtgccca | ggaggttctc | cggcacctgc | ggcaggagga | aaagggaagag | 1200 |
| gttactgtgg | gcagcttgaa | gacctcagcg | gtgcccagta | cctccacgat | gtcccaagag  | 1260 |
| cctgagctcc | tcacagtg   | aatggaaaag | cccctccctc | tcgcacgga  | tttctcttga  | 1320 |
| gaccaggggt | caccaggcca | gagcctccag | tggtctccaa | gcctctggac | tgggggctct  | 1380 |
| cttcagtggc | tgaatgtcca | gcagagctat | ttccttccac | agggggcctt | gcagggaagg  | 1440 |
| gtccaggact | tgacatctta | agatgcgtct | tgtccccttg | ggccagtcac | ttcccctctc  | 1500 |

|            |             |            |            |            |            |      |
|------------|-------------|------------|------------|------------|------------|------|
| tgagcctcgg | tgtcttcaac  | ctgtgaaatg | ggatcataat | cactgcctta | cctccctcac | 1560 |
| ggttggttg  | aggactgagt  | gtgtggaagt | ttttcataaa | ctttggatgc | tagtgtactt | 1620 |
| aggggggtg  | ccaggtgtct  | ttcatggggc | cttccagacc | cactccccac | ccttctcccc | 1680 |
| ttcctttgcc | cgggggacgc  | gaactctctc | aatggtatca | acaggctcct | tcgccctctg | 1740 |
| gctcctggtc | atgtttccatt | attggggagc | cccagcagaa | gaatggagag | gaggaggagg | 1800 |
| ctgagtttg  | ggtattgaat  | ccccgggctc | ccaccctgca | gcataaggt  | tgctatggac | 1860 |
| tctcctgccg | ggcaactctt  | gcgtaatcat | gactatctct | aggattctgg | caccacttcc | 1920 |
| ttccttgccc | ccttaagcct  | agctgtgtat | cggcaccccc | acccactag  | agtactccct | 1980 |
| ctcacttgcg | gtttccttat  | actccacccc | tttctcaacg | gtcctttttt | aaagcacatc | 2040 |
| tcagattaaa | aaaaaaaaaa  | aaaaaaaaaa | agggggggcn | gcnt       |            | 2084 |

&lt;210&gt; 235

&lt;211&gt; 2143

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2058)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2080)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2115)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2132)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 235

|             |             |            |            |             |             |      |
|-------------|-------------|------------|------------|-------------|-------------|------|
| tcgacccacg  | cgtcgggttg  | aattccttga | cctgcaaaca | catattttatt | agcctgactc  | 60   |
| aaacaatgaa  | gctattaaaa  | cttcggagga | acattgtaaa | actctctttg  | tatcggcatt  | 120  |
| tcaccaaacac | gcttattttg  | gcagtggcag | catccattgt | gtttatcatc  | tggacaacca  | 180  |
| tgaagttcag  | aatagtgaca  | tgtcagtcgg | actggcggga | gctgtgggta  | gacgatgcca  | 240  |
| tctggcgctt  | gctgttctcc  | atgatcctct | ttgtcatcat | ggttctctgg  | cgaccatctg  | 300  |
| caaacaacca  | gaggtttgcc  | ttttcaccat | tgtctgagga | agaggaggag  | gatgaacaaa  | 360  |
| aggagcctat  | gctgaaagaa  | agctttgaag | gaatgaaaat | gagaagtacc  | aaacaagaac  | 420  |
| ccaatggaaa  | tagtaaagt   | aacaaagcac | aggaagatga | tttgaagtgg  | gtagaagaga  | 480  |
| atgttccttc  | ttctgtgaca  | gatgtagcac | ttccagccct | tctggattca  | gatgaggaac  | 540  |
| gaatgatcac  | acactttgaa  | aggtcacaaa | tggagtaagg | aatgggaaga  | tttgagttta  | 600  |
| aagatggcta  | ccatcaggga  | agagatcagc | atctgtgtca | gtcttctgta  | cggctccatg  | 660  |
| ggattaaagg  | aagcaatgac  | atcctgatct | gttccttgat | ctttgggcat  | tggagttggc  | 720  |
| gagaggtgtc  | agaacaaaga  | gaacatctta | ctgaaaacaa | gttcataaga  | tgagaaaaat  | 780  |
| ctacgagctt  | cttattttaca | acactgctgc | cccctttcct | cccagactct  | gacatggatg  | 840  |
| ttcatgcaac  | ttaagtgtgt  | tgttcctgaa | ctttctgtaa | tgtttcattt  | tttaaactctg | 900  |
| acaaactaaa  | aagtttaacg  | tcttctaaaa | gattgtcatc | aacaccataa  | tatgtaatct  | 960  |
| ccaggagcaa  | ctgcctgtaa  | tttttattta | tttagggagt | tacatagggtg | atgggggaaa  | 1020 |
| ttgttaacta  | ccttttcattt | tcctgggaag | tcaaggttac | atcttgcaga  | ggttgttttg  | 1080 |
| agaaaaaagg  | gcccttctga  | gttaaggagc | catagttcta | tcaatgatca  | aaagaaaaaa  | 1140 |
| aaaaaaaaaga | gaaactgtta  | cagtatgatt | cagatcattt | aaaaaagcaa  | aatcaagtgc  | 1200 |

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| aatthttgtht | acaaatgggt  | tatattaaag  | atthtttctat | ttcagatgta  | ctthtaaagag | 1260 |
| aaatattagc  | ttaactcttt  | tgacatctgc  | tattgtgaca  | catcccatg   | ctggcaatgt  | 1320 |
| ggtgcacact  | ccgaaacttt  | taactactgt  | tttgaagcc   | tccaagggtg  | gcattgcagg  | 1380 |
| gtccttaggc  | aatgttttgt  | ttgcctttat  | gcagagaggt  | gctccaagtg  | ctgtgattga  | 1440 |
| gcaccgtgct  | agaggaactg  | taatgcttca  | gaagttgtag  | cttatacaaa  | ggaaacaggt  | 1500 |
| cctgctggct  | taattttaaac | agttattgca  | tgaagtagcg  | tggaggccct  | ggactgctgc  | 1560 |
| tcgttcttta  | ggatggactg  | ttctgggtatc | tggattgggt  | ttagagactg  | ttataaaggg  | 1620 |
| acatcacaag  | gtgatgggat  | tcatttgaag  | cactctatth  | ctgttttaat  | ggthtttatcc | 1680 |
| aatthttgcct | tccaagatt   | ttgtttctac  | ataaaaaggt  | catgccactt  | tttaataataa | 1740 |
| aaaaatttaa  | caaaattaat  | gtatthtttct | cattthtttct | aaactthttc  | ttaaagactct | 1800 |
| ttctgtcaaa  | ctcatgaaaa  | atthtcttct  | atggctthtta | ttctagattg  | tcttatthttc | 1860 |
| tgthaaaacc  | aatgaccaca  | tgaccacaat  | cttcactaac  | tcatactgca  | gtgaaagtgt  | 1920 |
| taacccttag  | gtagthttctc | tacaactctt  | tgctatgggt  | atthtttaaaa | aagthttccta | 1980 |
| gggaagtatc  | tctgagggaa  | caggcaatct  | gaaggaactg  | actatattct  | ccatggctaa  | 2040 |
| gtccattagg  | ccaaaagnct  | gggtgggtat  | tggtgtgtcan | gctgtctatt  | ggcatattaa  | 2100 |
| aaacgtaggc  | cgganggaat  | aattaggttg  | tnatgccggc  | ggg         |             | 2143 |

&lt;210&gt; 236

&lt;211&gt; 1133

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (528)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (552)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1133)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 236

|            |            |             |             |             |             |      |
|------------|------------|-------------|-------------|-------------|-------------|------|
| ggcacagctt | ggaatgaacc | cctgtggata  | aggggggacta | ttagatagaa  | taaacatcaa  | 60   |
| taaatgcttg | atgaataaac | gctaataccta | ccttcccagc  | ctgacacctc  | ccagtggaca  | 120  |
| ccacacttca | cttgaagcct | tagaaacctt  | tcccacccat  | gcttccagcc  | ctggcttcat  | 180  |
| gttgccatth | ctcaccceca | gaacaggccg  | cccgcctgaa  | gaaactacaa  | gagcaagaga  | 240  |
| aacaacagaa | agtggagtht | cgtaaaaagga | tggagaagga  | ggtgtcagat  | ttcattcaag  | 300  |
| acagtgggca | gatcaagaaa | aagthttcagc | caatgaacaa  | gatcgagagg  | agcatactac  | 360  |
| atgatgtgg  | ggaagtggct | ggcctgacat  | ccttctcctt  | tggggaagat  | gatgactgtc  | 420  |
| gctatgtcat | gatcttcaaa | aaggagtht   | caccctcaga  | tgaagagcta  | gactcttacc  | 480  |
| gtcgtggaga | ggaatgggac | cccagaagg   | ctgaggagaa  | gcggaacntg  | aaggagctgg  | 540  |
| cccagaggca | angaggagga | ggcagcccag  | caggggcctg  | tgggtgtgag  | ccctgcccagc | 600  |
| gactacaagg | acaagtacag | ccacctcatc  | ggcaaggagg  | cagccaaaaga | cgcagcccac  | 660  |
| atgctacagg | ccaataagac | ctacggctgt  | ktgcccgtgg  | ccaataagag  | ggacacacgc  | 720  |
| tccattgaag | aggctatgaa | tgagatcaga  | gccaaagaagc | gtctgcggca  | gagtggggaa  | 780  |
| gagthggcgc | caacctccta | ggcgccccgc  | ccagctccct  | ttgacccctg  | gggcagggca  | 840  |
| gggggcagg  | agagacaagg | ctgctgtctat | tagagcccat  | cctggagccc  | cacctctgaa  | 900  |
| ccacctccta | ccagctgtcc | ctcaggctgg  | gggaaaacag  | gtgtttgatt  | tgtcacctgt  | 960  |
| ggagcttgg  | tatgtgcgtg | gcatgtgtgt  | gtgtgtgtga  | gagtgtgaat  | gcacaggtgg  | 1020 |
| gtatttaatc | tgtattatth | cccgttcttg  | gaattthctt  | cccatggggc  | tgggggtactt | 1080 |
| tacattcaat | aaatactgtt | taacccaaaa  | aaaaaaaaaa  | aaaagaaaga  | agn         | 1133 |



<210> 237  
 <211> 1025  
 <212> DNA  
 <213> Homo sapiens

<400> 237  
 cctggccac attgcttcat tggcctggcc atgcccctgt actatggcag ccgctagtcc 60  
 ctgacaactt ccaccctgat tccggaccct gtagattggg cggcaccacc agatccccct 120  
 cccaggcctt cctccctctc ccatcagcag ccctgtaaca agtgccttgt gagaaaagct 180  
 ggagaagtga gggcagccag gttattctct ggagggttgg ggatgaaggg gtaccctagg 240  
 agatgtgaag tgtgggtttg gtttaaggaaa tgcttaccat cccccacccc caaccaagtt 300  
 cttccagact aaagaattaa ggtaacatca atacctaggc ctgagaaata accccatcct 360  
 tgttgggcag ctccctgctt tgcctgcat gaacagagtt gatgaaagtg ggggtgtggc 420  
 aacaagtggc tttccttgcc tacttttagtc acccagcaga gccactggag ctggctagt 480  
 cagcccagcc atgggtgcag actcttccat aagggtacct cacccttcca ctttcatgca 540  
 agaaggccca gttgcccacag attatacaac cattaccxaa accactctga cagtctctc 600  
 cagttccagc aatgcctaga gacatgctcc ctgcccctct caccagtgtg cttccccac 660  
 ctagcctttg ttctggaaac cccagagagg gctgggcttg actcatctca gggaatgtag 720  
 cccctgggccc ctggcttaag ccgacactcc tgacctctct gttcaccctg agggctgtct 780  
 tgaagccgcg taccactctc gaggtccta ggaggtagca tgcttccac tctggggcct 840  
 gccctgcctc agcagtctcc cagctcccaa cagcctgggg aagctctgca cagagtgacc 900  
 tgagaccagg tacaggaaac ctgtagctca atcagtgtct ctttaactgc ataagcaata 960  
 agatcttaat aaagtcttct aggtgttagg gtggttccca caaccacagc caaaaaaaaa 1020  
 aaaaa 1025

<210> 238  
 <211> 1400  
 <212> DNA  
 <213> Homo sapiens

<400> 238  
 ggcacagttt attaatacct attatgggaa agtcactttg gttggcattg aaaattacat 60  
 catctttaaa gcagtatttg tcccagatg gactcatcac tagcaaagac taggttcatt 120  
 ggaaggcata gggtagaga atgggaagat gragtggagg cgggttgta aagtgtgtc 180  
 agtgagtgat tttgtctact tgaataatgg tccatgtttg ggggcatatt gtgtttcata 240  
 agaagtgaag ggtatttgca aagtaagcta caaatgaccc ataaatctgt taacaacagt 300  
 ccttaatatg caaagatgaa aaacaagcat tactgtctacc caaagggaac tgggtgcttg 360  
 tgatgtgcag atggggctgt tggtaagag agctattaca ggttttctct cttaggtttc 420  
 ataggaggta gttactgaga tgagattggt ttatcttttt gaatacagat ctctgtctt 480  
 gagttagtct tgaggatggg agtaataaag gagttttttg tttttttgtt tgtttgtttg 540  
 ttttggtccc ttagtaatac tcctctgaca tttatttcta ttattcttca aagaaaggaa 600  
 accaactgaa atgtttgctt taacaaacat ttttaataagt tctctgggtt tttttttccc 660  
 ctttttaaaa aattagcata taccatagca ataaaagaac taatgttaac tattgtatgc 720  
 tacaacttaa gtgatttttc taaagaagca caatgtcatt graagtatta ttgaaaagga 780  
 tcatagtcac attgaatttg tgaaggccaa agaaattgaa gggagtata ttttcatttt 840  
 atgatattca catatttagt aaattttgtg tacaagaata ccaggcagag tgtttttacc 900  
 atggaaacag gtttcagatt actttgtttt tactgttaga gtctcaagtt tagaaatgct 960  
 aacacttaaa tcagtttttt tctcactata cttgaagatt gttaatatct tgatatcttc 1020  
 ctagcttgat ggaattttaa catatcttca gatctgtgac agtgacagcc aataggactg 1080  
 ataatttag cttcaaacca ataatatcca gggttaaaat aaaaatcata gtgaaagtac 1140  
 gattgtaaaa ttatgtctata ttaactttta agtctgtaac aacttgacat caaaatgtta 1200  
 tgtaattacc ataaataatg gctagcgaga acatcttttg aaattctcaa attacctttc 1260  
 ttactacact gtttgagaa tgaatgtaga aatgatcctg ttagctttct gaatgttctg 1320  
 ttggtgaatg tgtttttgct taaataaagc ttttgggtatt tgttttaaatw aaaaaaaaaa 1380  
 aaaaaaaaaa aaaaactcga 1400

<210> 239  
 <211> 1250  
 <212> DNA  
 <213> Homo sapiens

<400> 239  
 gccacgcgt ccgcccacgc gtccggcggt gcgagatg gggcgctgat ggccatggag 60  
 ggctactggc gcttcctggc gcygctggg tggcactgc tgcgcggctt cctgtcgggtg 120  
 atsttcgccc tgcgtctgggt cctccactac cgagaggggc ttggctggga tgggagcgca 180  
 ctagagttaa actggcaccc agtgctsatg gtcaccggct tgcgtctcat ccagggcac 240  
 gcatcatcgt ctacagactg ccgtggacct ggaaatgcag caagctcctg atgaaatcca 300  
 tccatgcagg gttaaatgca gttgctgcca ttcttgcaat tatctctgtg gtggccgtgt 360  
 ttgagaacca caatgttaac aatatagcca atatgtacag tctgcacagc tgggttgga 420  
 tgatagctgt catatgctat ttgttacagc ttctttcagg tttttcagtc tttctgcttc 480  
 catgggctcc gctttctctc cgagcatttc tcatgcccac acatgtttat tctggaattg 540  
 tcatcttttg aacagtgatt gcaacagcac ttatgggatt gacagagaaa ctgatttttt 600  
 ccctgagaga tcctgcatac agtacattcc cgccagaagg tgttttcgta aatacgcttg 660  
 gccttctgat cctgggtgttc ggggccctca ttttttgat agtcaccaga ccgcaatgga 720  
 aacgtcctaa ggagccaaat tctaccattc ttcatccaaa tggaggcact gaacaggag 780  
 caagagggttc catgccagcc tactctggca acaacatgga caaatcagat tcagagttaa 840  
 acartgaagt agcagcaagg aaaagaaact tagctctgga tgaggctggg cagagatcta 900  
 ccatgtaaaa tgttgtagag atagagccat ataacgtcac gtttcaaaac tagctctaca 960  
 gttttgcttc tcctattagc catatgataa ttgggctatg tagtatcaat atttacttta 1020  
 atcacaaagg atgggtttctt gaaataattt gtattgattg aggcctatga actgacctga 1080  
 attggaaagg atgtgattaa tataaataat agcagatata aattgtgggt atgttacctt 1140  
 tatcttggtt aggaccacaa cattagcacg gtgccttggt cakaatagat actcaatag 1200  
 tgaatatgtg tctactagta gttaattgga taaactggca gcatccctga 1250

<210> 240  
 <211> 1307  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (651)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1064)  
 <223> n equals a,t,g, or c

<400> 240  
 ggcacgagag aaaagagggt gagaatgttt tctagcaggc agaattgtgca tacatgtttt 60  
 catgartgtc ctttgggtgc tgtttctttt aaatcctctg tgcacagggc tctggccttt 120  
 artaaactgt ttttctgtct tacgtcatgc tgactgggtg ctaggggctg attacaaagg 180  
 ggaagagttg aacagacatc agggggccgat gaaaccaaag gactaggagt caggagaaca 240  
 agtcagggat taggagacag cgggtttggtt tattgttatc cagctggagg actcctaggg 300  
 gcagcagcag gaggaatacc agggccacgg aggggcagga gtctcacagt ggagggcaga 360  
 ctctaacaga tgccagctga acgctcgctg gccctggatg tcatacagat tggggaccag 420  
 aaatctgggc tcagagaacc cgtccagga gatttgaagc catgggttat cttctagagt 480  
 tgatactgat aatatatttt aatttttatt gatgtttaat accttctgaa acaggagggt 540  
 aagatcagat ggggaagcccy tctgttgaag gatcttggga accttgggtg tttttttttt 600  
 ttggtttttt tttttttgat cgagctgtgg acatccttct taattcgatt ntgaggattt 660

157

|             |             |            |            |             |             |      |
|-------------|-------------|------------|------------|-------------|-------------|------|
| gtttaactaa  | aaagttccca  | aacacagaaa | gggcctcccc | acctgctttg  | gggagctgtc  | 720  |
| tgtsetggga  | gtgccaggca  | tccsatggga | cccatcactg | ccagtgtctg  | tgccctcccag | 780  |
| aggtcagccc  | tgtgtctgcc  | ctggctctgt | ctcctctgtg | acagggcaga  | gcattttctgg | 840  |
| tcagttttctc | catgggtgcct | ccccccctt  | tgtaaagtgg | atggacatga  | tggaattcag  | 900  |
| ttgtctcacc  | ctgatagcct  | gggtgttgat | attcacttta | cccgactca   | gacacaggcg  | 960  |
| accttgaagc  | agttctcggt  | gtgtagagtc | cacgtgacag | tccccacagc  | ctccccagat  | 1020 |
| agctgtgtgc  | ctgtgcgcta  | ctgctgtgcc | attttcccaa | cttnggcgtt  | tcactaaatg  | 1080 |
| cagctgatct  | ctctctctgt  | gcactcgtga | tccatgttga | acaatacatg  | taggtttcttt | 1140 |
| ttccacgcaa  | tgtaagaaca  | tgatatactg | tacgttgga  | agcatttacc  | ttatttatat  | 1200 |
| acctgaatgt  | tcctactaca  | caaataaaca | tatattaaat | wctaaaaaaaa | aaaaaaaaaa  | 1260 |
| ctggaggggg  | ggcccgggtac | ccaaatcgcc | ggatagtgat | cgtaaac     |             | 1307 |

&lt;210&gt; 241

&lt;211&gt; 888

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (830)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 241

|            |            |            |            |             |            |     |
|------------|------------|------------|------------|-------------|------------|-----|
| ctgttagaat | gcccagttta | cctggatggc | aacccaacag | tgctcctgcc  | cacctgcccc | 60  |
| tcaatcctcc | tagaattcag | cccccaattg | cccagttacc | aataaaaaact | tgtacaccag | 120 |
| ccccagggac | agtctcaaat | gcaaatccac | agagtgasmc | accacctcgg  | gtagaatttg | 180 |
| atgacaacaa | tccctttagt | gaaagttttc | aagaacggga | acgtaaggaa  | cgtttacgag | 240 |
| aacagcaaga | gagacaacgg | atccaactca | tgcaggaggt | agatagacaa  | agagctttgc | 300 |
| agcagaggat | ggaaatggag | cagcatggta | tggtgggctc | tgagataagt  | agtagtagga | 360 |
| catctgtgtc | ccagattccc | ttctacagtt | ccgacttacc | ttgtgatttt  | atgcaacctc | 420 |
| taggacctct | tcagcagtct | ccacaacacc | aacagcaa   | ggggcagggt  | ttacagcagc | 480 |
| agaatataca | acaaggatca | attaattcac | cctccacca  | aactttcatg  | cagactaatg | 540 |
| agcgaggcag | gtaggccctc | cttcatttgt | tcttgattca | ccatcaatcc  | ctgttggaag | 600 |
| cccaaatttt | tcttctgtga | agcagggaca | tggaaatcct | tctgggacca  | gcttccagca | 660 |
| gtccccagtg | aggccttctt | ttacacctgc | tttaccagca | gcacctccag  | tagctaatag | 720 |
| cagtctccca | tgtggccaag | attctactat | aacccatgga | cacagttatc  | cgggatcaac | 780 |
| ccaatcgctc | attcagttgt | attctgatat | aatcccagag | gaaaaagggn  | aaaaaaaaa  | 840 |
| amaaraaara | araaaggaga | tgatgatgca | gaattccacc | aaggctcc    |            | 888 |

&lt;210&gt; 242

&lt;211&gt; 1811

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

<222> (16)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1810)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1811)  
 <223> n equals a,t,g, or c

<400> 242  
 cngncagtag cgggtcngatt cccgggtcga cccacgcgtc cgtgtcattc cagggccttt 60  
 cagtggcttt cattctgaag ttcttgata acatgttcca tgtcttgatg gccaggtta 120  
 ccastgtcat tatcacaaca gtgtctgtcc tgggtcttga ctccaggccc tccctggaat 180  
 ttttcttggga agccscatca gtctstctct ctatatttat ttataatgcc agcaagcctc 240  
 aagttccgga atacgcacct aggcgaagaa ggatccgaga tctaagtggc aatctttggg 300  
 agcgttccag tggggatgga gaagaactag aaagacttac caaacccaag agtgatgagt 360  
 cagatgaaga tactttttaa ctgggtaccca catagtttgc agctctcttg aaccttattt 420  
 tcacattttc agtgtttgta atatttatct ttccactttg ataaaccaga aatgtttcta 480  
 aatcctaata ttctttgcat atatctagct actccctaaa tgggtccatc caaggcttag 540  
 agtaccctaaa ggctaagaaa ttctaaagaa ctgatacagg agtaacaata tgaagaattc 600  
 attaatatct cagtacttga taaatcagaa agttatatgt gcagattatt ttcttggcc 660  
 ttcaagcttc caaaaaactt gtaataatca tgttagctat agcttgata tacacataga 720  
 gatcaatttg ccaaatattc acaatcatgt agttctagt tacatgccaa agtcttcctt 780  
 ttttaacatt ataaaagcta ggttgtctct tgaattttga ggccctagag atagtcattt 840  
 tgcaagtaaa gagcaacggg accctttcta aaaacgttgg ttgaaggacc taaatacctg 900  
 gccataccat agatttgga tgatgtatgc tgtgtctaaat attttgctga agaagcagtt 960  
 tctcagacac aacatctcag aatttttaatt tttagaaatt catgggaaat tggatttttg 1020  
 taataatctt ttgatgtttt aaacattggg tccctagtca ccatagttac cacttgattt 1080  
 ttaagtcatt taaacaagcc acgggtgggc tttttctcc tcagtttgag gagaaaaatc 1140  
 ttgatgtcat tactcctgaa ttattacatt ttggagaata agagggcatt ttattttatt 1200  
 agttactaat tcaagctgtg actattgtat atctttccaa gagttgaaat gctggcttca 1260  
 gaatcatacc agattgtcag tgaagctgat gcctaggaac ttttaaaggg atcctttcaa 1320  
 aaggatcact tagcaaacac atgttgactt ttaactgatg tatgaatatt aatactctaa 1380  
 aaatagaaaag accagtaata tataagtcac ttacagtgac tacttcacac ttaaaagtgc 1440  
 atggtatttt tcatggtatt ttgcatgcag ccagttaact ctgtagata gagaagtgcag 1500  
 gtgatagatg atattaaaaa ttagcaaaaca aaagtgaact gctcagggtc atgcagctgg 1560  
 gtgatgatag aagagtgggc tttaactggc aggcctgtat gtttacagac taccatactg 1620  
 taaatatgag ctttatgggtg tcattctcag aaacttatac atttctgctc tccctttctc 1680  
 taagtttcat gcagatgaat ataaggtaat atactattat ataattcatt tgtgatatcc 1740  
 acaataatat gactggcaag aattggtgga aatttgtaat taaaataatt attaaaccta 1800  
 aaaaaaaaaa n 1811

<210> 243  
 <211> 2271  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (553)  
 <223> n equals a,t,g, or c

<220>

<221> SITE  
 <222> (2267)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2269)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2271)  
 <223> n equals a,t,g, or c

<400> 243

|             |             |             |            |             |            |      |
|-------------|-------------|-------------|------------|-------------|------------|------|
| ctgacctcat  | ggcgtagagc  | ctagcaacag  | cgcaggctcc | cagccgagtc  | cgttatggcc | 60   |
| gctgcggtcc  | cgaagaggat  | gagggggcca  | gcacaagcga | aactgctgcc  | cgggtcggcc | 120  |
| atccaagccc  | ttgtgggggt  | ggcgcggccg  | ctggctcttg | cgctcctgct  | tgtgtccgcc | 180  |
| gctctatcca  | gtgttgtatc  | acggactgat  | tcaccgagcc | caaccgtact  | caactcacat | 240  |
| ttttctaccc  | caaatgtgaa  | tgttttaaca  | catgaaaacc | aaaccaaacc  | ttctatttcc | 300  |
| caaatcagca  | ccacctccc   | ttccacgacg  | agtaccaaga | aaagtggagg  | agcatctgtg | 360  |
| gtccctcatc  | cctcgctac   | tcctctgtct  | caagaggaag | ctgataacaa  | tgaagatcct | 420  |
| agtatagagg  | aggaggatct  | tctcatgctg  | aacagttctc | catccacagc  | caaagacact | 480  |
| ctagacaatg  | gcgattatgg  | agaaccagac  | tatgactgga | ccacggggcc  | cagggacgac | 540  |
| gacgagtctg  | atngacacct  | tggagaaaa   | caggggttac | atggaaattg  | aacagtcagt | 600  |
| gaaatctttt  | aagatgccat  | cctcaaatat  | agaagaggaa | gacagccatt  | tcttttttca | 660  |
| tcttattatt  | tttgcttttt  | gcattgctgt  | tgtttacatt | acatatcaca  | acaaaaggaa | 720  |
| gatttttctt  | ctggttcaaa  | gcaggaaatg  | gcgtgatggc | ctttgttcca  | aaacagtggg | 780  |
| ataccatcgc  | ctagatcaga  | atgttaatga  | ggcaatgcct | tctttgaaga  | ttaccaatga | 840  |
| ttatattttt  | taaagcactg  | tgatttgaat  | ttgcttatgt | aattttatgt  | gcttgacttt | 900  |
| ttatatgata  | ttgtgcaaat  | gtttgccata  | ggcaattggg | acttaaatga  | gaggtgagtc | 960  |
| tctcttttgc  | cttgggtgctt | tggaaattaa  | atgtcacaaa | cgagtatata  | attttttatc | 1020 |
| tgtactttta  | gagctgagtt  | taatcagggt  | tccaaaatgt | gagttaaaca  | ttaccttata | 1080 |
| tttactctgt  | tagtttttat  | tgttttagat  | tattatgtct | tcttctggaa  | gtattagtga | 1140 |
| tgtacttttt  | aaaagatccc  | aaacttgtaa  | ctaaattctg | acatatctgt  | tactgctgac | 1200 |
| tcacattcat  | tctccgccat  | tcaataacta  | ttttttatcc | acattttttt  | ttgttcccaa | 1260 |
| actgtaatgt  | acaaggatat  | gtgtgataat  | gctttggatt | tgagtaatat  | ttttttttct | 1320 |
| tccaagaaaa  | ctgcttttga  | tattttttaga | taattttaa  | ataatttagg  | ataatgatat | 1380 |
| tgctcaatct  | gaccacaatt  | ttaggtaaaa  | cattaaatgt | gtcaagaaat  | cttggcaaca | 1440 |
| gagactctgc  | agcttgacgt  | ggacatagat  | aaaatgttac | agagataacta | tttttttggg | 1500 |
| tggaaattact | atattaaaat  | tagaagcaga  | aactggtaaa | atgttaaata  | catgtacaat | 1560 |
| tgcttttagt  | tagcaattga  | ttgtagcatg  | ggttcctcca | aggtttcaag  | caatgggcag | 1620 |
| agtttaaaat  | tatatcagat  | tcgtttactt  | cgtttattat | tttacagtaa  | atttgaataa | 1680 |
| atcttagggg  | tcattatcac  | ttaaataata  | ctgtacctag | gtcttttcaa  | ttaaaattat | 1740 |
| acctgaatga  | agttgtttgt  | atacataaag  | gatattttgt | tacaattacc  | ttttttcccc | 1800 |
| cacacttggt  | ttctttgttt  | ttgtttttta  | tggcaactgg | aaagtattta  | ctatgggatt | 1860 |
| cattttatgt  | tgtctttcta  | tcataaagaa  | ttgatcaata | tgtaaatatg  | tgatttgaac | 1920 |
| catggttgac  | ttacaagtgt  | cactacagct  | ttttagaaaa | catagcccta  | atatatgtta | 1980 |
| agcaggaccc  | gggtgagcca  | gtgggcttgc  | gctttatgta | gagctggaag  | aaggccgtcc | 2040 |
| atcctgtctc  | ttgggcggac  | agtgtacttt  | cctaataagg | aagggaagca  | caatggaaat | 2100 |
| acccctgaac  | cgttttattg  | cagtaatttt  | tttcatatct | gaaactatta  | tttaattttt | 2160 |
| tgaataagat  | tttaaaaaat  | aaatggcaaa  | gatataaatc | taaaaaaaaa  | aaaaaaaaaa | 2220 |
| aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa | aaaaaanana  | n          | 2271 |

<210> 244  
 <211> 2500  
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2459)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2473)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2475)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2478)

<223> n equals a,t,g, or c

<400> 244

|                                   |                        |             |      |
|-----------------------------------|------------------------|-------------|------|
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| ggcggcggtg agaagagcga ggcgkaggag  | gggggtgcat ggccgggcag  | cagttccagt  | 120  |
| acgatgacag tgggaacacc ttcttctact  | tcctcacctc cttcgtgggg  | ctcatcgtga  | 180  |
| tcccggcgac atactacctc tggccccgag  | atcagaatgc cgagcaaatt  | cgattaaaaga | 240  |
| atatcagaaa agtatatgga aggtgtatgt  | ggtacgttta cggttattaa  | aaccccagcc  | 300  |
| aaatattatt cctacagtaa agaaaatagt  | tctgcttgca ggatgggcat  | tgttcttatt  | 360  |
| ccttgcatat aaagtttcca aaacagaccg  | agaataccaaa gaatacaatc | cttatgaagt  | 420  |
| attaaaatttg gatcctggag ccacagtagc | agaaattaaa aaacaatatc  | gtttgctgtc  | 480  |
| acttaaatat catccagata aaggaggtga  | tgaggttatg ttcatgagga  | tagcaaaagc  | 540  |
| ttatgctgct ttaacggatg aagagtcccg  | gaaaaattgg gaagaatttg  | gaaatccaga  | 600  |
| tgggcctcaa gccacaagct ttggaattgc  | cctgccagct tggatagttg  | accagaaaaa  | 660  |
| ttcaattctg gttttacttg tatatggatt  | ggcatttatg gttatccttc  | cagttgttgt  | 720  |
| gggctcttgg tggatcgcct caatacgcta  | tagtgagagc cagattctaa  | tacgsacaac  | 780  |
| acagatttat acatactttg tttataaaac  | ccgaaatatg gatatgaaac  | gtcttatcat  | 840  |
| ggttttggst ggagcttctg aatttgatcc  | tcagtataat aaagatgcca  | caagcagacc  | 900  |
| aacggataat attctaatac cacagctaag  | cagagaaatt ggcagcatta  | atttaaagaa  | 960  |
| gaatgagcct ccacttacct gcccatatag  | cctgaaggcc agagttcttt  | tactgtctca  | 1020 |
| tcttgctaga atgaaaattc ctgagaccct  | tgaagaagat cagcaattca  | tgctaaaaaa  | 1080 |
| gtgtcctgcc ctacttcaag aaatgggttaa | tgtaatctgc caactaatag  | taatggcccg  | 1140 |
| gaaccgtgaa gaaagggagt ttctgtctcc  | aactttggca tccctagaaa  | actgcatgaa  | 1200 |
| gctttctcag atggccgttc agggacttca  | gcaatttaag tctccccttc  | tgcatgctcc  | 1260 |
| tcattattgaa gaggacaatc ttagacgggt | ttctaatacat aagaagtata | aaattaaaac  | 1320 |
| tatccaggat ttggtgagtt taaaagaatc  | agatcgtcac actctactgc  | acttccttga  | 1380 |
| agatgaaaaa tatgaagagg ttatggctgt  | ccttgggagt tttccatatg  | tgaccatgga  | 1440 |
| tataaaatca caggtgttag atgatgaaga  | tagcaacaac atcacagtag  | gacaccttagt | 1500 |
| tacagtgttg gtttaagttga caaggcaaac | aatggctgaa gtattttgaaa | aggagcagtc  | 1560 |
| catctgtgct gcagaggaac agccagcaga  | agatgggcag ggtgaaacta  | acaagaacag  | 1620 |
| gacaaaagga ggatggcaac agaagagtaa  | aggacccaag aaaactgcta  | aatcaaaaaa  | 1680 |
| aaagaaacct ttaaaaaaaa aacctacacc  | tgtgctatta ccacagtcaa  | agcaacagaa  | 1740 |
| acaaaagcag gcaaatggag tcgttgggaa  | tgaagctgca gtaaaggaag  | atgaagaaga  | 1800 |
| agtttcagat aagggcagtg attctgaaga  | agaagaaacc aatagagatt  | cccaaagtga  | 1860 |
| gaaagatgat ggtagtgaac gagactctga  | tagagagcaa gatgaaaaac  | aaaacaaaga  | 1920 |
| tgatgaagca gagtggcaag aattacaaca  | aagcatagag cgaaaagaga  | gagctctatt  | 1980 |
| ggaaacccaa tcaaaaataa cacatcctgt  | gtatagcctt tacttttctg  | aggaaaaaca  | 2040 |
| agaatggttg tggttttaca ttgcagatag  | gaaggagcag acattaatat  | ccatgccata  | 2100 |

161

|             |            |             |             |            |            |      |
|-------------|------------|-------------|-------------|------------|------------|------|
| tcattgtgtgt | acgctgaaag | atacagagga  | ggttagagctg | aagtttcctg | caccaggcaa | 2160 |
| gcctggaaat  | tatcagtata | ctgtgtttct  | gagatcagac  | tcctatatgg | gtttggatca | 2220 |
| gattaaacca  | ttggaagttk | ggaagtcat   | gaggctgaag  | cctgtgccag | aaaatcacc  | 2280 |
| acagtgggat  | acagcaatag | agggggatga  | agaccaggag  | gacagtgagg | gctttgaaga | 2340 |
| tagctttgag  | ggaggaagag | ggagggagga  | aggaaggtgg  | tggacttaag | gcagttactc | 2400 |
| tggaatggga  | cccacagtgt | tttgcaccat  | atthttggcaa | ttttttttgc | ccgtttttng | 2460 |
| gaagtgtttt  | ccntnaancc | caggaacccat | tacagaaccg  |            |            | 2500 |

&lt;210&gt; 245

&lt;211&gt; 1338

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (133)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (867)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1338)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 245

|             |            |             |             |            |             |      |
|-------------|------------|-------------|-------------|------------|-------------|------|
| cttccgggttc | tccgggcagc | tgccactgct  | gtagcttctg  | ccacctgcca | cgaccggggcc | 60   |
| tctccctggc  | gtttggtcac | ctctgcttca  | ttctccaccg  | cgcctatggt | ccctcttgga  | 120  |
| gccagcgtgg  | cgngcctggc | ggctcccggg  | tggtgagaga  | gcggtccggg | aacgatgaag  | 180  |
| gcctcgcagt  | gctgctgctg | tctcagccac  | ctcttggtct  | ccgtcctcct | cctgctgttg  | 240  |
| ctgctgaac   | taagcgggyc | cctggmagtc  | ctgctgcagg  | cagccgaggc | cgcgccaggt  | 300  |
| yttgggcctc  | ctgaccctag | accaggacat  | taccgcccgt  | gccaccgggc | cctwaccctt  | 360  |
| gccagcagc   | cgggccgtgg | tctggctgaa  | gctgcggggg  | ccgcggggct | ccgagggagg  | 420  |
| caatggcagc  | aaccctgtgg | ccgggcttga  | gacggacgat  | cacggaggga | aggccgggga  | 480  |
| argctcggtg  | ggtggcggcc | ttgctgtgag  | ccccaaacct  | ggcgacaagc | ccatgaccca  | 540  |
| gcgggcccctg | accgtgttga | tggtggtgag  | cggcgcgggtg | ctggtgtact | tcgtggtcag  | 600  |
| gacggtcagg  | atgagaagaa | gaaaccgaaa  | gactaggaga  | tatggagtgt | tggacactaa  | 660  |
| catagaaaat  | atggaattga | cacctttaga  | acaggatgat  | gaggatgatg | acaacacgtt  | 720  |
| gtttgatgcc  | aatcatcctc | gaagataaga  | atgtgccttt  | tgatgaaaga | actttatctt  | 780  |
| tctacaatga  | agagtggaa  | ttctatgttt  | aaggaataag  | aagccactat | atcaatgttg  | 840  |
| ggggggtatt  | taagttacat | atatttnaac  | aacctttaat  | ttgctgttgc | aataaatacc  | 900  |
| gtatcctttt  | attatatctt | tatatgtata  | gaagtactct  | gttaatgggc | tcagagatgt  | 960  |
| tggggataaa  | gtatactgta | ataattttatc | tgtttgaaaa  | ttactataaa | acggtgtttt  | 1020 |
| ctgrtcgggt  | tttgtttcct | gcttaccata  | tgattgtaaa  | ttgttttatg | tattaatcag  | 1080 |
| ttaatgctaa  | ttatttttgc | tgatgtcata  | tgttaaagag  | ctataaatte | caacaaccaa  | 1140 |
| ctggtgtgta  | aaaataattt | aaaatytctt  | ttactgaaag  | gtatttccca | tttttgtggg  | 1200 |
| gaaaagaagc  | caaatttatt | actttgtgtt  | ggggttttta  | aaatattaag | aaatgtctaa  | 1260 |
| gttattgttt  | gcaaaacaat | aaatatgatt  | ttaaattctc  | ttaaaaaaaa | aaaaaaaaac  | 1320 |
| cccggggggg  | ggcccggn   |             |             |            |             | 1338 |

&lt;210&gt; 246

&lt;211&gt; 654

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (651)

<223> n equals a,t,g, or c

<400> 246

|            |             |             |            |             |             |     |
|------------|-------------|-------------|------------|-------------|-------------|-----|
| gaattcggca | cgaggcagct  | tgtgcttta   | aggaggtgtt | caaagcatgt  | ctgagcagag  | 60  |
| acttttgggc | tctgttttaa  | ttaatacttt  | aaaataattc | atatttaaaa  | tatcaratgt  | 120 |
| ttccataaag | aggaggatgt  | ttaaatgcct  | ccagactaca | ttccttttta  | ttsccttgatt | 180 |
| ttacctggga | gtccaaagtt  | caattcccat  | aaagcaagcg | ttttatttgt  | cactttcaat  | 240 |
| atacatccga | ttgccatgct  | taagatgcaa  | tatgggctgc | ggaaataggt  | taaccacag   | 300 |
| gctcccaggg | cccagtgtag  | aagggtgagag | attcgtgtaa | aatgattcaa  | ataaaaggaa  | 360 |
| gaccctggcc | gggtgccgta  | rtcacgcct   | gtaatcccag | cactttggga  | ggccgaagcg  | 420 |
| agtggatgac | gagggttagga | gttggagacc  | agcctggcca | acatcgtgaa  | accccgctctc | 480 |
| tactaaaaat | acaaaaatta  | gccgggcatg  | gtggcaggca | cctgtaatcc  | tagctagttg  | 540 |
| ggaggctgag | gcaggagaat  | cgtttgaatc  | tgggagttgg | aggttggtcag | tgagctgaga  | 600 |
| tcgcgccaca | gcactccagc  | ctgggtgaca  | gggtgagact | ctgtctcaaa  | naga        | 654 |

<210> 247

<211> 1146

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (35)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (36)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (37)

<223> n equals a,t,g, or c

<400> 247

|             |            |            |            |            |            |     |
|-------------|------------|------------|------------|------------|------------|-----|
| aaaaaaaaacc | caggggaacn | ttgggggccc | ctttnnnttc | cccctccagg | ccattgggga | 60  |
| attcttcaag  | ttaatcctgc | tttgctcttg | gccaacaggg | cttgtagggg | ggagagaccc | 120 |
| aggatcatca  | aggggttcga | gtgcaagcct | cactcccagc | cctggcaggg | agccctgttc | 180 |
| gagaagacgc  | ggctactctg | tggggcgacg | ctcatcgccc | ccagatggct | cctgacagca | 240 |
| gcccactgcc  | tcaagccccg | ctacatagtt | cacctggggc | agcacaaact | ccagaaggag | 300 |
| gagggctgtg  | agcagacccg | gacagccact | gagtccttcc | cccaccccg  | cttcaacaac | 360 |
| agcctcccga  | acaaagacca | ccgcaatgac | atcatgctgg | tgaagatggc | atcgccagtc | 420 |
| tccatcacct  | gggctgtgcg | accctcacc  | ctctcctcac | gctgtgtcac | tgctggcacc | 480 |
| agctgyctca  | tttccggctg | gggcagmacg | tccagcccc  | agttacgcct | gcctcacacc | 540 |
| ttgsgatgcg  | ccaacatcac | catcattgag | caccagaagt | gtgagaacgc | ctaccccggc | 600 |
| aacatcacag  | acaccatggt | gtgtgccagc | gtgcaggaag | ggggcaagga | ctcctgccag | 660 |



163

|            |             |            |            |            |            |      |
|------------|-------------|------------|------------|------------|------------|------|
| ggtgactccg | ggggccctct  | ggtctgtaac | cagtctcttc | aaggcattat | ctcctggggc | 720  |
| caggatccgt | gtgcgatcac  | ccgaaagcct | ggtgtctaca | cgaaagtctg | caaatatgtg | 780  |
| gactggatcc | aggagacgat  | gaagaacaat | tagactggac | ccaccaccca | cagcccatca | 840  |
| ccctccattt | ccacttgggtg | tttggttcct | gttcactctg | ttaataagaa | accctaagcc | 900  |
| aagaccctct | acgaacattc  | tttgggcctc | ctggactaca | ggagatgctg | tcacttaata | 960  |
| atcaacctgg | ggttcgaaat  | cagtgagacc | tggattcaaa | ttctgccttg | aaatattgtg | 1020 |
| actctgggaa | tgacaacacc  | tggtttgttc | tctgttgat  | ccccagcccc | aaagacagct | 1080 |
| cctggccata | tatcaaggtt  | tcaataaata | tttgctaaat | gaaaaaaaaa | aaaaaaaaaa | 1140 |
| actcga     |             |            |            |            |            | 1146 |

&lt;210&gt; 248

&lt;211&gt; 1443

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (776)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (907)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1288)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 248

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| ataaactgaa  | ataggtcatg  | caaatataaa  | atattatttt  | taaattattt  | gtcataagaa  | 60   |
| acgatgggtg  | ccatattttg  | ctttaataat  | ggaaaaaatg  | tggtagcat   | tctktggaag  | 120  |
| gtggatcatca | gatagtagac  | atthttctagg | atthttttct  | acctgcatat  | gtggaaatgt  | 180  |
| gtactacttt  | agatttatwt  | aatggcagct  | aactcagagg  | catcaaaatg  | tgctaattggt | 240  |
| gtaatatggc  | ctttgtcttg  | ctgtyctggt  | ttgtargcct  | tcaatcaagc  | argggcaggg  | 300  |
| ccgtacagtg  | aacttgcct   | ttgscagacg  | ccagcgtctg  | cccctgaccc  | cgtctccact  | 360  |
| ctctgtgtcc  | tggaggagga  | gccccttgat  | gcytaccctg  | attcaccttc  | tgcggtgcctt | 420  |
| gtactgaact  | gggaagagcc  | gtgcaataac  | ggatctgaaa  | tccttgctta  | caccattgat  | 480  |
| ctaggagaca  | ctagcattac  | cgtgggcaac  | accaccatgc  | atggttatgaa | agatctcctt  | 540  |
| ccagaaacca  | cctaccggtg  | agtgaagggt  | agtagaaatc  | tgcacagca   | catcagcact  | 600  |
| tggggatcta  | agtaaacctc  | tgggggaaaa  | tgaccaagtg  | gatgtcatct  | cccagctggt  | 660  |
| tctaagagcc  | cagatgtcca  | gagtattgtc  | tcaccttgat  | ccctcaggcc  | agaagacctg  | 720  |
| tgaaaaagcc  | acactggttc  | agggactcac  | tggacgggtt  | tgtgtccact  | ytaacntgca  | 780  |
| ccgtctctac  | cccagagtgg  | actcaratcc  | tcaagtcatt  | ctctgaacat  | tgrrgtcaga  | 840  |
| aattataaaa  | gggctttggc  | aatatgttag  | cccaagaatt  | tggcttcttc  | cagaaattgt  | 900  |
| gccgacntta  | acagtggctt  | aaatgatggt  | aaaactttta  | agattttctaa | aaggrtggca  | 960  |
| ttggagatac  | ggtgactttt  | attaaacmac  | ctatagttgt  | ttaatgaytt  | ctaaaaaat   | 1020 |
| atctggagct  | cagggttcca  | actgggggaa  | cacatgttga  | gratcattgt  | ttactaatta  | 1080 |
| aatgccaggt  | aaccggttga  | aattatcaaa  | aacatcttcc  | acgtaccaga  | aagcacctca  | 1140 |
| gaggatagtt  | ctgttatgga  | gaagatgaaa  | tggtttagta  | gtgtaggaac  | tatggaaagg  | 1200 |
| tgagcttaga  | tttggtatgt  | aaaacctcaa  | gacctatttt  | aaaaagtatt  | ttatgaatgc  | 1260 |
| agcataaata  | atttaattca  | gtgttaanat  | gccaaaggcta | gtatattgag  | ctgaatgtga  | 1320 |
| aaagaaactc  | acattggggag | aatgccacct  | tttctttata  | agatagcttt  | gaagatacca  | 1380 |
| tttagacag   | atggaaattg  | aatagcttta  | gaaaaggcaa  | atgtttgatc  | ttgggggaaa  | 1440 |
| aaa         |             |             |             |             |             | 1443 |

164

<210> 249  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals stop translation

<400> 249  
 Met Leu Ser Thr Gly Ile Glu Val Ala Arg Pro Pro Ala Thr Leu Leu  
           1                  5                  10                  15  
 Gly Leu Met Phe Val Leu Thr Gly Met Pro Arg Gly Leu Arg Xaa  
                   20                  25                  30

<210> 250  
 <211> 116  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (78)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (116)  
 <223> Xaa equals stop translation

<400> 250  
 Met Asn Val Val Ile Val Ile Ile Leu Phe Ser Phe Asp Ser Val Gly  
           1                  5                  10                  15  
 Thr Met Phe Ser Cys Asn Arg Ile Pro Lys Ile Thr Val Leu Asn Lys  
                   20                  25                  30  
 Leu Lys Phe Xaa Cys Glu Val Leu Leu Arg Ile Gln Thr Ile Gln Gly  
           35                  40                  45  
 Phe Tyr Arg Cys Thr Arg Ile Ser Arg Tyr Lys Gly Ile Phe Pro Asp  
           50                  55                  60  
 Phe Cys Gln Ser Gln Cys Met Gly Cys Asn Pro Glu Ser Xaa Met Ala  
           65                  70                  75                  80  
 Val Pro Ala Leu Val Thr Pro Ile Leu Ala His Arg Lys Lys Glu Lys  
                   85                  90                  95

165

Gly Met Cys Leu Phe Thr Leu Ile Ile Ala Pro Thr Arg Cys Thr His  
                   100                                  105                                  110

Tyr Phe Cys Xaa  
                   115

<210> 251  
 <211> 103  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (103)  
 <223> Xaa equals stop translation

<400> 251  
 Met Ser Ser Ala Lys Ile Val Arg Gln Arg Gly Ala Val Pro Thr Tyr  
   1                                  5                                  10                                  15

Tyr Thr Thr Glu Ala Gly Glu Ile Ile Phe Leu Val Leu Asn Trp Ser  
                   20                                  25                                  30

Leu Ser Ile Leu His Ile Val Asp Val Leu Cys Ser Lys Pro Glu Lys  
                   35                                  40                                  45

Ser Val Thr Glu Asp Ala Ala Ser Gly Leu Ser Gln Arg Met Thr Ala  
                   50                                  55                                  60

Leu Val Trp Arg Lys Gly Pro Asp Gly Gly Ser Arg Lys Pro Ile Leu  
                   65                                  70                                  75                                  80

Leu Leu Phe Phe Phe Leu Pro Leu Ile Leu Cys Phe His Ser Phe Ile  
                                   85                                  90                                  95

His Ser Ser Asn Ile Cys Xaa  
                   100

<210> 252  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (13)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (22)

166

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 252

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Leu | Phe | Pro | Gln | Xaa | Ala | Leu | Arg | Leu | Gly | Xaa | Trp | Pro | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Trp | Ser | Ile | Leu | Xaa | Lys | Tyr | Ser | Val | Asn | Phe | Phe | Ser | Ala | Tyr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Pro | Met | Gly | Ala | Val | Gly | Thr | Glu | Phe |
|     |     | 35  |     |     |     |     | 40  |     |     |

<210> 253

<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals stop translation

<400> 253

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Ile | Leu | Leu | Leu | Phe | Met | Leu | Leu | Asn | Asn | Val | Val | Leu | Val |
| 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Asp | Asn | Cys | Gln | Arg | Lys | Asn | Thr | Val | Gln | Glu | Arg | Arg | Xaa |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| Trp | Ser | Gln | Trp | Xaa |
|     |     |     | 35  |     |

<210> 254

<211> 128

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (128)

<223> Xaa equals stop translation

167

&lt;400&gt; 254

Met Ala Ala Xaa Pro Pro Gly Cys Thr Pro Pro Xaa Leu Leu Asp Ile  
 1 5 10 15

Ser Trp Leu Thr Glu Ser Leu Gly Ala Gly Gln Pro Val Pro Val Glu  
 20 25 30

Cys Arg His Arg Leu Glu Val Ala Gly Pro Arg Lys Gly Pro Leu Ser  
 35 40 45

Pro Ala Trp Met Pro Ala Tyr Ala Cys Gln Arg Pro Thr Pro Leu Thr  
 50 55 60

His His Asn Thr Gly Leu Ser Glu Leu Leu Glu His Gly Val Cys Glu  
 65 70 75 80

Glu Val Glu Arg Val Arg Arg Ser Glu Arg Tyr Gln Thr Met Lys Val  
 85 90 95

Arg Arg Ala Gly Leu Gly Pro Thr Pro Gly Met Ser Cys Pro Gly Asn  
 100 105 110

Asp Asn Thr Val His Thr Met His Gly Glu Ala Asn Arg Gly Ser Xaa  
 115 120 125

&lt;210&gt; 255

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (67)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 255

Met Ser Ile Leu Cys Cys Pro Xaa Leu Cys Leu Phe Phe Ser Phe Cys  
 1 5 10 15

Ile Ser Ser Gly Ser Cys Pro Phe Ser His Val Ser Gln Leu Ser Phe  
 20 25 30

Ile Ala Thr Phe Ser Gln Ser Ser Pro Val Leu Leu Val Pro Ala Tyr  
 35 40 45

Asn Thr Tyr Leu Ser Phe Leu Ala Phe Leu Asp Cys Ala Ser Leu Thr  
 50 55 60

168

Ser Thr Xaa  
65

<210> 256  
<211> 69  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (69)  
<223> Xaa equals stop translation

<400> 256  
Met Ser Thr Phe Gln Leu Leu Leu Leu Ile Leu Ala Gln Ser Thr Tyr  
1 5 10 15  
Lys Ile Lys Ser Lys Pro Leu His Met Thr Asn His Thr Leu Leu Asn  
20 25 30  
Ser Pro Gly Leu Asn Pro Ser Ser Pro Thr Leu Asn Phe Lys Thr Gln  
35 40 45  
Gln His Glu Ser Val Ser Tyr Ala Cys Cys His Met Arg Ser Leu His  
50 55 60

His Ala Phe Ala Xaa  
65

<210> 257  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (36)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (37)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 257  
Met Val Ser Val Val Leu Ile Phe Ser Phe Leu Ser Leu Thr Ile Ser  
1 5 10 15  
Thr Thr Ala Ser Ala Tyr Asn Gly Asn Asp Thr Gln Gly Trp Asn Asp  
20 25 30

169

Lys Phe His Xaa Xaa Ser Val Lys Thr Gln Thr Xaa  
           35                          40

<210> 258  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (51)  
 <223> Xaa equals stop translation

<400> 258  
 Met Ile Ser Asp Ala Gly Ala Gly Phe Gly Val Phe Leu Leu Val Pro  
   1                  5                  10                  15

Arg Ala Gly His Cys Trp Gly Ala Gly Lys Pro Leu Pro Ser Cys Pro  
                   20                  25                  30

Ser Val Ala Ser Ile Pro Ser Trp Val Leu Pro Ser Phe Leu Glu Arg  
           35                  40                  45

Gly Arg Xaa  
       50

<210> 259  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 259  
 Met Val Gln Thr Ile Gln Asp Phe Leu Ser Leu Phe Ser Thr Pro Ile  
   1                  5                  10                  15

Phe Leu Leu Leu Leu Met Phe Glu Thr Leu Ser Leu Ala Pro Ala Trp  
                   20                  25                  30

Leu Lys Pro Leu Arg Val Thr Ser His Ser Xaa  
           35                  40

<210> 260  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals stop translation

170

&lt;400&gt; 260

```

Met Ile Leu Met Pro Gly Leu Gly Thr Ser Arg Gln Arg Ser Val Pro
 1             5             10             15

Phe Val Pro Thr Leu Asn Ala Ser Thr Pro Gly Ala Met Thr Gly Pro
             20             25             30

Thr Ala Thr Leu Thr Ser Cys Gln Trp Thr Thr Ala Cys Arg Val Ser
             35             40             45

Trp Ala Asn Gly Trp Thr Ser Leu Arg Thr Phe Arg Xaa
 50             55             60

```

&lt;210&gt; 261

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 261

```

Met Ser His His Ala Gln Pro Arg Phe Leu Leu Ile Thr Met Leu Leu
 1             5             10             15

Gln Glu Ala Lys Pro Val Ser Asn Ile Pro His Leu Leu Glu Ser Trp
             20             25             30

Tyr Phe Gly Xaa
             35

```

&lt;210&gt; 262

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 262

```

Met Asn Ser Leu Phe Trp Met Ile Leu Leu Pro Val Ser Gln Asp Gln
 1             5             10             15

Val Val Glu Gly Leu Gln Gly Gly Phe Ser Gln Ile His Met Arg Ile
             20             25             30

Leu Arg Lys His Leu Xaa
             35

```

&lt;210&gt; 263



171

<211> 211  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (5)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (211)  
 <223> Xaa equals stop translation

<400> 263

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Arg | Ser | Xaa | Asp | Val | Thr | Asn | Thr | Thr | Phe | Leu | Leu | Met | Ala | 1   | 5   | 10  | 15  |
| Ala | Ser | Ile | Tyr | Leu | His | Asp | Gln | Asn | Pro | Asp | Ala | Ala | Leu | Arg | Ala | 20  | 25  | 30  |     |
| Leu | His | Gln | Gly | Asp | Ser | Leu | Glu | Cys | Thr | Ala | Met | Thr | Val | Gln | Ile | 35  | 40  | 45  |     |
| Leu | Leu | Lys | Leu | Asp | Arg | Leu | Asp | Leu | Ala | Arg | Lys | Glu | Leu | Lys | Arg | 50  | 55  | 60  |     |
| Met | Gln | Asp | Leu | Asp | Glu | Asp | Ala | Thr | Leu | Thr | Gln | Leu | Ala | Thr | Ala | 65  | 70  | 75  | 80  |
| Trp | Val | Ser | Leu | Ala | Thr | Gly | Gly | Glu | Lys | Leu | Gln | Asp | Ala | Tyr | Tyr | 85  | 90  | 95  |     |
| Ile | Phe | Gln | Glu | Met | Ala | Asp | Lys | Cys | Ser | Pro | Thr | Leu | Leu | Leu | Leu | 100 | 105 | 110 |     |
| Asn | Gly | Gln | Ala | Ala | Cys | His | Met | Ala | Gln | Gly | Arg | Trp | Glu | Ala | Ala | 115 | 120 | 125 |     |
| Glu | Gly | Leu | Leu | Gln | Glu | Ala | Leu | Asp | Lys | Asp | Ser | Gly | Tyr | Pro | Glu | 130 | 135 | 140 |     |
| Thr | Leu | Val | Asn | Leu | Ile | Val | Leu | Ser | Gln | His | Leu | Gly | Lys | Pro | Pro | 145 | 150 | 155 | 160 |
| Glu | Val | Thr | Asn | Arg | Tyr | Leu | Ser | Gln | Leu | Lys | Asp | Ala | His | Arg | Ser | 165 | 170 | 175 |     |
| His | Pro | Phe | Ile | Lys | Glu | Tyr | Gln | Ala | Lys | Glu | Asn | Asp | Phe | Asp | Arg | 180 | 185 | 190 |     |
| Leu | Val | Leu | Gln | Tyr | Ala | Pro | Ser | Ala | Glu | Ala | Gly | Pro | Glu | Leu | Ser | 195 | 200 | 205 |     |
| Gly | Pro | Xaa |     |     |     |     |     |     |     |     |     |     |     |     |     | 210 |     |     |     |

172

<210> 264  
 <211> 548  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (548)  
 <223> Xaa equals stop translation

<400> 264

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Asp | Ser | Glu | Ala | Leu | Gly | Phe | Glu | His | Met | Gly | Leu | Asp | Pro | 1   | 5   | 10  | 15  |
| Arg | Leu | Leu | Gln | Ala | Val | Thr | Asp | Leu | Gly | Trp | Ser | Arg | Pro | Thr | Leu | 20  | 25  | 30  |     |
| Ile | Gln | Glu | Lys | Ala | Ile | Pro | Leu | Ala | Leu | Glu | Gly | Lys | Asp | Leu | Leu | 35  | 40  | 45  |     |
| Ala | Arg | Ala | Arg | Thr | Gly | Ser | Gly | Lys | Thr | Ala | Ala | Tyr | Ala | Ile | Pro | 50  | 55  | 60  |     |
| Met | Leu | Gln | Leu | Leu | Leu | His | Arg | Lys | Ala | Thr | Gly | Pro | Val | Val | Glu | 65  | 70  | 75  | 80  |
| Gln | Ala | Val | Arg | Gly | Leu | Val | Leu | Val | Pro | Thr | Lys | Glu | Leu | Ala | Arg | 85  | 90  | 95  |     |
| Gln | Ala | Gln | Ser | Met | Ile | Gln | Gln | Leu | Ala | Thr | Tyr | Cys | Ala | Arg | Asp | 100 | 105 | 110 |     |
| Val | Arg | Val | Ala | Asn | Val | Ser | Ala | Ala | Glu | Asp | Ser | Val | Ser | Gln | Arg | 115 | 120 | 125 |     |
| Ala | Val | Leu | Met | Glu | Lys | Pro | Asp | Val | Val | Val | Gly | Thr | Pro | Ser | Arg | 130 | 135 | 140 |     |
| Ile | Leu | Ser | His | Leu | Gln | Gln | Asp | Ser | Leu | Lys | Leu | Arg | Asp | Ser | Leu | 145 | 150 | 155 | 160 |
| Glu | Leu | Leu | Val | Val | Asp | Glu | Ala | Asp | Leu | Leu | Phe | Ser | Phe | Gly | Phe | 165 | 170 | 175 |     |
| Glu | Glu | Glu | Leu | Lys | Ser | Leu | Leu | Cys | His | Leu | Pro | Arg | Ile | Tyr | Gln | 180 | 185 | 190 |     |
| Ala | Phe | Leu | Met | Ser | Ala | Thr | Phe | Asn | Glu | Asp | Val | Gln | Ala | Leu | Lys | 195 | 200 | 205 |     |
| Glu | Leu | Ile | Leu | His | Asn | Pro | Val | Thr | Leu | Lys | Leu | Gln | Glu | Ser | Gln | 210 | 215 | 220 |     |
| Leu | Pro | Gly | Pro | Asp | Gln | Leu | Gln | Gln | Phe | Gln | Val | Val | Cys | Glu | Thr | 225 | 230 | 235 | 240 |
| Glu | Glu | Asp | Lys | Phe | Leu | Leu | Leu | Tyr | Ala | Leu | Leu | Lys | Leu | Ser | Leu | 245 | 250 | 255 |     |

173

Ile Arg Gly Lys Ser Leu Leu Phe Val Asn Thr Leu Glu Arg Ser Tyr  
 260 265 270  
 Arg Leu Arg Leu Phe Leu Glu Gln Phe Ser Ile Pro Thr Cys Val Leu  
 275 280 285  
 Asn Gly Glu Leu Pro Leu Arg Ser Arg Cys His Ile Ile Ser Gln Phe  
 290 295 300  
 Asn Gln Gly Phe Tyr Asp Cys Val Ile Ala Thr Asp Ala Glu Val Leu  
 305 310 315 320  
 Gly Ala Pro Val Lys Gly Lys Arg Arg Gly Arg Gly Pro Lys Gly Asp  
 325 330 335  
 Lys Ala Ser Asp Pro Glu Ala Gly Val Ala Arg Gly Ile Asp Phe His  
 340 345 350  
 His Val Ser Ala Val Leu Asn Phe Asp Leu Pro Pro Thr Pro Glu Ala  
 355 360 365  
 Tyr Ile His Arg Ala Gly Arg Thr Ala Arg Ala Asn Asn Pro Gly Ile  
 370 375 380  
 Val Leu Thr Phe Val Leu Pro Thr Glu Gln Phe His Leu Gly Lys Ile  
 385 390 395 400  
 Glu Glu Leu Leu Ser Gly Glu Asn Arg Gly Pro Ile Leu Leu Pro Tyr  
 405 410 415  
 Gln Phe Arg Met Glu Glu Ile Glu Gly Phe Arg Tyr Arg Cys Arg Asp  
 420 425 430  
 Ala Met Arg Ser Val Thr Lys Gln Ala Ile Arg Glu Ala Arg Leu Lys  
 435 440 445  
 Glu Ile Lys Glu Glu Leu Leu His Ser Glu Lys Leu Lys Thr Tyr Phe  
 450 455 460  
 Glu Asp Asn Pro Arg Asp Leu Gln Leu Leu Arg His Asp Leu Pro Leu  
 465 470 475 480  
 His Pro Ala Val Val Lys Pro His Leu Gly His Val Pro Asp Tyr Leu  
 485 490 495  
 Val Pro Pro Ala Leu Arg Gly Leu Val Arg Pro His Lys Lys Arg Lys  
 500 505 510  
 Lys Leu Ser Ser Ser Cys Arg Lys Ala Lys Arg Ala Lys Ser Gln Asn  
 515 520 525  
 Pro Leu Arg Ser Phe Lys His Lys Gly Lys Lys Phe Arg Pro Thr Ala  
 530 535 540  
 Lys Pro Ser Xaa  
 545

174

&lt;210&gt; 265

&lt;211&gt; 299

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 265

Met Thr Thr Val Pro Pro Ser Pro Arg Pro Met Ser Arg Pro Ser Glu  
 1 5 10 15

Arg Asn Met Arg Arg Pro Arg Gly Pro Ser Pro Leu Pro Ala Ser Pro  
 20 25 30

Arg Asn Ser Thr Pro Asp Glu Pro Asp Val His Phe Ser Lys Lys Phe  
 35 40 45

Leu Asn Val Phe Met Ser Gly Arg Ser Arg Ser Ser Ser Ala Glu Ser  
 50 55 60

Phe Gly Leu Phe Ser Cys Ile Ile Asn Gly Glu Glu Gln Glu Gln Thr  
 65 70 75 80

His Arg Ala Ile Phe Arg Phe Val Pro Arg His Glu Asp Glu Leu Glu  
 85 90 95

Leu Glu Val Asp Asp Pro Leu Leu Val Glu Leu Gln Ala Glu Asp Tyr  
 100 105 110

Trp Tyr Glu Ala Tyr Asn Met Arg Thr Gly Ala Arg Gly Val Phe Pro  
 115 120 125

Ala Tyr Tyr Ala Ile Glu Val Thr Lys Glu Pro Glu His Met Ala Ala  
 130 135 140

Leu Ala Lys Asn Ser Asp Trp Val Asp Gln Phe Arg Val Lys Phe Leu  
 145 150 155 160

Gly Ser Val Gln Val Pro Tyr His Lys Gly Asn Asp Val Leu Cys Ala  
 165 170 175

Ala Met Gln Lys Ile Ala Thr Thr Arg Arg Leu Thr Val His Phe Asn  
 180 185 190

Pro Pro Ser Ser Cys Val Leu Glu Ile Ser Val Arg Gly Val Lys Ile  
 195 200 205

Gly Val Lys Ala Asp Asp Ser Gln Glu Ala Lys Gly Asn Lys Cys Ser  
 210 215 220

His Phe Phe Gln Leu Lys Asn Ile Ser Phe Cys Gly Tyr His Pro Lys  
 225 230 235 240

Asn Asn Lys Tyr Phe Gly Phe Ile Thr Lys His Pro Ala Asp His Arg  
 245 250 255

Phe Ala Cys His Val Phe Val Ser Glu Asp Ser Thr Lys Ala Leu Ala  
 260 265 270

175

Glu Ser Val Gly Arg Ala Phe Gln Gln Phe Tyr Lys Gln Phe Val Glu  
275 280 285

Tyr Thr Cys Pro Thr Glu Asp Ile Tyr Leu Glu  
290 295

```
<210> 266
<211> 40
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>  
<221> SITE  
<222> (40)  
<223> Xaa equals stop translation
```

<400> 266  
Leu Leu Tyr Leu Leu Lys Val Xaa Val Ile Phe Val Phe Ser Ser Ser  
1 5 10 15

Lys Gly Val Thr Leu Val Ser Met Asn Leu Thr Ser Phe Phe Val Ser  
20 25 30

Ser Val Leu Ala Cys Phe Ser, Xaa  
35 40

```
<210> 267
<211> 594
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (99)
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 267  
Met Pro Ala Ser Ser Leu Glu Ser Arg Ser Phe Leu Leu Ala Lys Lys  
1 5 10 15

Ser Gly Glu Asn Val Ala Lys Phe Ile Ile Asn Ser Tyr Pro Lys Tyr  
20 25 30

Phe Gln Lys Asp Ile Ala Glu Pro His Ile Pro Cys Leu Met Pro Glu  
35 40 45

Tyr Phe Glu Pro Gln Ile Lys Asp Ile Ser Glu Ala Ala Leu Lys Glu  
50 55 60

Arg Ile Glu Leu Arg Lys Val Lys Ala Ser Val Asp Met Phe Asp Gln  
65 70 75 80

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Leu | Leu | Gln | Ala | Gly | Thr | Thr | Val | Ser | Leu | Glu | Thr | Thr | Asn | Ser | Leu |  |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Leu | Asp | Xaa | Leu | Cys | Tyr | Tyr | Gly | Asp | Gln | Glu | Pro | Ser | Thr | Asp | Tyr |  |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| His | Phe | Gln | Gln | Thr | Gly | Gln | Ser | Glu | Ala | Leu | Glu | Glu | Glu | Asn | Asp |  |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| Glu | Thr | Ser | Arg | Arg | Lys | Ala | Gly | His | Gln | Phe | Gly | Val | Thr | Trp | Arg |  |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| Ala | Lys | Asn | Asn | Ala | Glu | Arg | Ile | Phe | Ser | Leu | Met | Pro | Glu | Lys | Asn |  |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| Glu | His | Ser | Tyr | Cys | Thr | Met | Ile | Arg | Gly | Met | Val | Lys | His | Arg | Ala |  |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| Tyr | Glu | Gln | Ala | Leu | Asn | Leu | Tyr | Thr | Glu | Leu | Leu | Asn | Asn | Arg | Leu |  |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| His | Ala | Asp | Val | Tyr | Thr | Phe | Asn | Ala | Leu | Ile | Glu | Ala | Thr | Val | Cys |  |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| Ala | Ile | Asn | Glu | Lys | Phe | Glu | Glu | Lys | Trp | Ser | Lys | Ile | Leu | Glu | Leu |  |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| Leu | Arg | His | Met | Val | Ala | Gln | Lys | Val | Lys | Pro | Asn | Leu | Gln | Thr | Phe |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| Asn | Thr | Ile | Leu | Lys | Cys | Leu | Arg | Arg | Phe | His | Val | Phe | Ala | Arg | Ser |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| Pro | Ala | Leu | Gln | Val | Leu | Arg | Glu | Met | Lys | Ala | Ile | Gly | Ile | Glu | Pro |  |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| Ser | Leu | Ala | Thr | Tyr | His | His | Ile | Ile | Arg | Leu | Phe | Asp | Gln | Pro | Gly |  |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| Asp | Pro | Leu | Lys | Arg | Ser | Ser | Phe | Ile | Ile | Tyr | Asp | Ile | Met | Asn | Glu |  |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| Leu | Met | Gly | Lys | Arg | Phe | Ser | Pro | Lys | Asp | Pro | Asp | Asp | Asp | Lys | Phe |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| Phe | Gln | Ser | Ala | Met | Ser | Ile | Cys | Ser | Ser | Leu | Arg | Asp | Leu | Glu | Leu |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| Ala | Tyr | Gln | Val | His | Gly | Leu | Leu | Lys | Thr | Gly | Asp | Asn | Trp | Lys | Phe |  |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
| Ile | Gly | Pro | Asp | Gln | His | Arg | Asn | Phe | Tyr | Tyr | Ser | Lys | Phe | Phe | Asp |  |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| Leu | Ile | Cys | Leu | Met | Glu | Gln | Ile | Asp | Val | Thr | Leu | Lys | Trp | Tyr | Glu |  |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |

177

Asp Leu Ile Pro Ser Ala Tyr Phe Pro His Ser Gln Thr Met Ile His  
 385 390 395 400  
 Leu Leu Gln Ala Leu Asp Val Ala Asn Arg Leu Glu Val Ile Pro Lys  
 405 410 415  
 Ile Trp Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu  
 420 425 430  
 Arg Glu Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu  
 435 440 445  
 Leu Gln Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr  
 450 455 460  
 Glu Ser Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser  
 465 470 475 480  
 Leu Asn Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu  
 485 490 495  
 Ala Trp Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg  
 500 505 510  
 Ser Glu Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser  
 515 520 525  
 Pro Ser Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu  
 530 535 540  
 Pro Ile Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile  
 545 550 555 560  
 Asn Gln Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser  
 565 570 575  
 Asp Ser Asp Thr Asp Ser Ser Ser Asp Ser Asp Ser Asp Thr Ser Glu  
 580 585 590

Gly Lys

&lt;210&gt; 268

&lt;211&gt; 131

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (131)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 268

Met Lys Leu Asn Leu Cys Ile Pro Asn Trp Ala Arg Cys Pro Leu Leu  
 1 5 10 15

Leu Leu Phe Pro Gln Leu Leu Pro Phe Gln Gly Glu Asp Asp Asp Pro

178

20                      25                      30  
 Leu Lys Ala Lys Ala Ala Asn Leu Val Glu Ala Val Pro Trp Gly Ile  
           35                      40                      45  
 Lys Ala Pro Ser Phe Gln Val Thr Cys Leu Val Arg Val Gln Leu Gln  
           50                      55                      60  
 Ser Cys Thr Pro Ser Arg Pro Ser Thr Leu Leu Ala Thr Ser Gln Ser  
           65                      70                      75                      80  
 Pro Gly Arg Ile Ser Cys Tyr Ser Pro Leu Ser His Leu Pro Pro Val  
                           85                      90                      95  
 Thr Thr Ser Ile Gln Pro Ser Pro Val Met Val Pro Phe Gln Tyr Gln  
                           100                      105                      110  
 Ala Phe Leu Leu Gln Val Lys Glu Pro Ala Ala Gln Thr Leu Leu Gly  
           115                      120                      125  
 Gln Gln Xaa  
           130

&lt;210&gt; 269

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 269

Met Arg Tyr His Ala Gln Leu Ile Phe Cys Ile Phe Cys Xaa Phe Val  
       1                      5                      10                      15

Phe Val Xaa Lys Xaa  
           20

&lt;210&gt; 270

&lt;211&gt; 159

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;



179

<221> SITE  
 <222> (109)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (118)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (122)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (127)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 270  
 Met Thr Gly Thr Tyr Ser Gly Gln Phe Val Met Glu Gly Phe Leu Asn  
   1                  5                  10                  15  
  
 Leu Lys Trp Ser Arg Phe Ala Arg Val Val Leu Thr Arg Ser Ile Ala  
                   20                  25                  30  
  
 Ile Ile Pro Thr Leu Leu Val Ala Val Phe Gln Asp Val Glu His Leu  
           35                  40                  45  
  
 Thr Gly Met Asn Asp Phe Leu Asn Val Leu Gln Ser Leu Gln Leu Pro  
   50                  55                  60  
  
 Phe Ala Leu Ile Pro Ile Leu Thr Phe Thr Ser Leu Arg Pro Val Met  
   65                  70                  75                  80  
  
 Ser Asp Phe Ala Asn Gly Leu Gly Trp Arg Ile Ala Gly Gly Ile Trp  
                   85                  90                  95  
  
 Ser Tyr His Leu Phe His His Met Tyr Phe Val Val Xaa Tyr Val Arg  
           100                  105                  110  
  
 Asp Leu Arg His Val Xaa Leu Tyr Val Xaa Ala Ala Val Val Xaa Arg  
   115                  120                  125  
  
 Gly Leu Ser Gly Leu Cys Val Leu Leu Gly Leu Ala Met Phe Asp Cys  
   130                  135                  140  
  
 Thr Gly His Val Leu Pro Gly Leu Trp Ala Tyr Gly Lys His Leu  
   145                  150                  155  
  
  
 <210> 271  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE

180

&lt;222&gt; (219)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 271

Met His Phe Leu Phe Arg Phe Ile Val Phe Phe Tyr Leu Trp Gly Leu  
 1 5 10 15

Phe Thr Ala Gln Arg Gln Lys Lys Glu Glu Ser Thr Glu Glu Val Lys  
 20 25 30

Ile Glu Val Leu His Arg Pro Glu Asn Cys Ser Lys Thr Ser Lys Lys  
 35 40 45

Gly Asp Leu Leu Asn Ala His Tyr Asp Gly Tyr Leu Ala Lys Asp Gly  
 50 55 60

Ser Lys Phe Tyr Cys Ser Arg Thr Gln Asn Glu Gly His Pro Lys Trp  
 65 70 75 80

Phe Val Leu Gly Val Gly Gln Val Ile Lys Gly Leu Asp Ile Ala Met  
 85 90 95

Thr Asp Met Cys Pro Gly Glu Lys Arg Lys Val Val Ile Pro Pro Ser  
 100 105 110

Phe Ala Tyr Gly Lys Glu Gly Tyr Ala Glu Gly Lys Ile Pro Pro Asp  
 115 120 125

Ala Thr Leu Ile Phe Glu Ile Glu Leu Tyr Ala Val Thr Lys Gly Pro  
 130 135 140

Arg Ser Ile Glu Thr Phe Lys Gln Ile Asp Met Asp Asn Asp Arg Gln  
 145 150 155 160

Leu Ser Lys Ala Glu Ile Asn Leu Tyr Leu Gln Arg Glu Phe Glu Lys  
 165 170 175

Asp Glu Lys Pro Arg Asp Lys Ser Tyr Gln Asp Ala Val Leu Glu Asp  
 180 185 190

Ile Phe Lys Lys Asn Asp His Asp Gly Asp Gly Phe Ile Ser Pro Lys  
 195 200 205

Glu Tyr Asn Val Tyr Gln His Asp Glu Leu Xaa  
 210 215

&lt;210&gt; 272

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

181

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 272

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Trp | Val | Ile | Arg | Val | Phe | Gln | Lys | Thr | Phe | Leu | Phe | Phe | Val | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Trp | Ser | Val | His | Cys | Ile | Ser | Asp | Lys | Phe | Gly | Cys | Leu | Trp | His |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Cys | Met | Lys | Arg | Glu | Gly | Asp | Xaa | Asn | Cys | Leu | Ser | Phe | Ser | Xaa |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |
|-----|-----|
| Leu | Xaa |
|     | 50  |

&lt;210&gt; 273

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (122)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 273

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Pro | Ser | Gln | Thr | Glu | Xaa | Phe | Ala | Ala | Cys | Gly | Gly | His | Ser | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Val | Xaa | Leu | Pro | Leu | Gly | Leu | Pro | Phe | Cys | Pro | Arg | Ala | Ala |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Cys | Asp | Leu | Pro | Phe | Ser | Leu | Pro | Ser | Phe | Pro | Gly | Gln | Ala | Arg |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Gly | Gly | Ala | Glu | Lys | Gln | Gly | Ala | Glu | Gly | Arg | Gly | Leu | Gln | Val |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Pro | Arg | Gly | Gln | Arg | Thr | Phe | Gln | Val | Ser | Arg | Thr | Ala | Pro | Ala |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

182

Ala Pro Arg Ser Arg Gln Pro Arg Pro Pro Ala Ala Leu Pro Ala Leu  
                     85                    90                    95  
 Gly Phe Gly Gly Arg Gly Val Ala Lys Gly Arg Phe Leu Cys Phe Trp  
                     100                    105                    110  
 Cys Leu Tyr Met Leu Arg Ile Asp Gln Xaa  
                     115                    120

<210> 274  
 <211> 88  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (53)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (88)  
 <223> Xaa equals stop translation

<400> 274  
 Met Thr Ala Phe Cys Ser Leu Leu Leu Gln Ala Gln Ser Leu Leu Pro  
   1                    5                    10                    15  
 Arg Thr Met Ala Ala Pro Gln Asp Ser Leu Arg Pro Gly Glu Glu Asp  
                     20                    25                    30  
 Glu Gly Met Gln Leu Leu Gln Thr Lys Asp Ser Met Ala Lys Gly Ala  
                     35                    40                    45  
 Arg Pro Gly Ala Xaa Arg Gly Arg Ala Arg Trp Gly Leu Ala Tyr Thr  
                     50                    55                    60  
 Leu Leu His Asn Pro Thr Leu Gln Val Phe Arg Lys Thr Ala Leu Leu  
   65                    70                    75                    80  
 Gly Ala Asn Gly Ala Gln Pro Xaa  
                     85

<210> 275  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (26)  
 <223> Xaa equals stop translation

<400> 275  
 Met Ile Gln Val Ser Val Pro Leu Leu Thr Ile Met Ile Phe Leu Leu

183

1 5 10 15  
Tyr Leu Gln Ile Gly Pro Gly Lys Leu Xaa  
20 25

<210> 276  
<211> 29  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (29)  
<223> Xaa equals stop translation

<400> 276  
Met Leu Leu Asp Pro Phe Ile Leu Leu Phe Cys Leu Phe Ser Thr Ala  
1 5 10 15  
Ala Gln Ser Cys Leu Glu Phe Ile Tyr Ile Gln Phe Xaa  
20 25

<210> 277  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (14)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 277  
Met Lys Phe Leu Ser Ile Leu Leu Asp Asp Asn Asn Phe Xaa Leu Met  
1 5 10 15  
Leu Met Leu Ala Pro Phe Gly Cys Leu Ala Phe Glu Arg Ser Met Lys  
20 25 30

Met Arg Asn Gly Ala Leu Gly Leu Glu Glu Val Xaa  
35 40

<210> 278  
<211> 363  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (307)

184

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (363)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 278

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Thr | Leu | Phe | Asn | Leu | Leu | Trp | Leu | Ala | Leu | Ala | Cys | Ser | Pro | 1   | 5   | 10  | 15  |
| Val | His | Thr | Thr | Leu | Ser | Lys | Ser | Asp | Ala | Lys | Lys | Ala | Ala | Ser | Lys | 20  | 25  | 30  |     |
| Thr | Leu | Leu | Glu | Lys | Ser | Gln | Phe | Ser | Asp | Lys | Pro | Val | Gln | Asp | Arg | 35  | 40  | 45  |     |
| Gly | Leu | Val | Val | Thr | Asp | Leu | Lys | Ala | Glu | Ser | Val | Val | Leu | Glu | His | 50  | 55  | 60  |     |
| Arg | Ser | Tyr | Cys | Ser | Ala | Lys | Ala | Arg | Asp | Arg | His | Phe | Ala | Gly | Asp | 65  | 70  | 75  | 80  |
| Val | Leu | Gly | Tyr | Val | Thr | Pro | Trp | Asn | Ser | His | Gly | Tyr | Asp | Val | Thr | 85  | 90  | 95  |     |
| Lys | Val | Phe | Gly | Ser | Lys | Phe | Thr | Gln | Ile | Ser | Pro | Val | Trp | Leu | Gln | 100 | 105 | 110 |     |
| Leu | Lys | Arg | Arg | Gly | Arg | Glu | Met | Phe | Glu | Val | Thr | Gly | Leu | His | Asp | 115 | 120 | 125 |     |
| Val | Asp | Gln | Gly | Trp | Met | Arg | Ala | Val | Arg | Lys | His | Ala | Lys | Gly | Leu | 130 | 135 | 140 |     |
| His | Ile | Val | Pro | Arg | Leu | Leu | Phe | Glu | Asp | Trp | Thr | Tyr | Asp | Asp | Phe | 145 | 150 | 155 | 160 |
| Arg | Asn | Val | Leu | Asp | Ser | Glu | Asp | Glu | Ile | Glu | Glu | Leu | Ser | Lys | Thr | 165 | 170 | 175 |     |
| Val | Val | Gln | Val | Ala | Lys | Asn | Gln | His | Phe | Asp | Gly | Phe | Val | Val | Glu | 180 | 185 | 190 |     |
| Val | Trp | Asn | Gln | Leu | Leu | Ser | Gln | Lys | Arg | Val | Thr | Asp | Gln | Leu | Gly | 195 | 200 | 205 |     |
| Met | Phe | Thr | His | Lys | Glu | Phe | Glu | Gln | Leu | Ala | Pro | Val | Leu | Asp | Gly | 210 | 215 | 220 |     |
| Phe | Ser | Leu | Met | Thr | Tyr | Asp | Tyr | Ser | Thr | Ala | His | Gln | Pro | Gly | Pro | 225 | 230 | 235 | 240 |
| Asn | Ala | Pro | Leu | Ser | Trp | Val | Arg | Ala | Cys | Val | Gln | Val | Leu | Asp | Pro | 245 | 250 | 255 |     |
| Lys | Ser | Lys | Trp | Arg | Ser | Lys | Ile | Leu | Leu | Gly | Leu | Asn | Phe | Tyr | Gly | 260 | 265 | 270 |     |

185

Met Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala  
 275 280 285

Arg Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp  
 290 295 300

Ser Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly  
 305 310 315 320

Arg His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu  
 325 330 335

Glu Leu Ala Arg Glu Leu Gly Val Gly Val Ser Ile Trp Glu Leu Gly  
 340 345 350

Gln Gly Leu Asp Tyr Phe Tyr Asp Leu Leu Xaa  
 355 360

&lt;210&gt; 279

&lt;211&gt; 128

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (128)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 279

Leu Pro Thr Lys Ile Leu Val Lys Pro Asp Arg Thr Phe Glu Ile Lys  
 1 5 10 15

Ile Gly Gln Pro Thr Val Ser Tyr Phe Leu Lys Ala Ala Ala Gly Ile  
 20 25 30

Glu Lys Gly Ala Arg Gln Thr Gly Lys Glu Val Ala Gly Leu Val Thr  
 35 40 45

Leu Lys His Val Tyr Glu Ile Ala Arg Ile Lys Ala Gln Asp Glu Ala  
 50 55 60

Phe Ala Leu Gln Asp Val Pro Leu Ser Ser Val Val Arg Ser Ile Ile  
 65 70 75 80

Gly Ser Ala Arg Ser Leu Gly Ile Arg Val Val Lys Asp Leu Ser Ser  
 85 90 95

Glu Glu Leu Ala Ala Phe Gln Lys Glu Arg Ala Ile Phe Leu Ala Ala  
 100 105 110

Gln Lys Glu Ala Asp Leu Ala Ala Gln Glu Glu Ala Ala Lys Lys Xaa  
 115 120 125

186

<210> 280  
<211> 54  
<212> PRT  
<213> Homo sapiens  
  
<220>  
<221> SITE  
<222> (54)  
<223> Xaa equals stop translation  
  
<400> 280  
Met Leu Leu Gln Ile His Pro Leu Leu Pro Ser Pro Thr Ile Pro His  
1 5 10 15  
  
Ile Leu Leu Leu Phe Leu Tyr Pro Thr Phe Ser Ile Leu Glu His Ser  
20 25 30  
  
Cys Ser Tyr Cys Ile Glu Tyr Leu Trp Val Cys Leu Leu Phe Cys Leu  
35 40 45  
  
Ser Leu Trp Phe Leu Xaa  
50

<210> 281  
<211> 29  
<212> PRT  
<213> Homo sapiens  
  
<220>  
<221> SITE  
<222> (26)  
<223> Xaa equals stop translation  
  
<400> 281  
Met Cys Leu Trp Cys Cys Gly Asp Val Cys Ser Gly Leu Ser Ser Leu  
1 5 10 15  
  
Leu Ser Leu Cys Val Cys Cys Val Val Leu Ala Val Cys  
20 25

<210> 282  
<211> 26  
<212> PRT  
<213> Homo sapiens  
  
<220>  
<221> SITE  
<222> (26)  
<223> Xaa equals stop translation  
  
<400> 282  
Glu Gly Leu Arg Leu Leu Leu Ser Leu Pro Ala Ala Leu Pro Arg Ser  
1 5 10 15  
  
Cys Cys His Pro Arg Trp Leu Pro Val Xaa  
20 25

<210> 283  
<211> 221



187

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 283

Met Phe His Gly Ile Pro Ala Thr Pro Gly Ile Gly Ala Pro Gly Asn  
 1 5 10 15

Lys Pro Glu Leu Tyr Glu Glu Val Lys Leu Tyr Lys Asn Ala Arg Glu  
 20 25 30

Arg Glu Lys Tyr Asp Asn Met Ala Glu Leu Phe Ala Val Val Lys Thr  
 35 40 45

Met Gln Ala Leu Glu Lys Ala Tyr Ile Lys Asp Cys Val Ser Pro Ser  
 50 55 60

Glu Tyr Thr Ala Ala Cys Ser Arg Leu Leu Val Gln Tyr Lys Ala Ala  
 65 70 75 80

Phe Arg Gln Val Gln Gly Ser Glu Ile Ser Ser Ile Asp Glu Phe Cys  
 85 90 95

Arg Lys Phe Arg Leu Asp Cys Pro Leu Ala Met Glu Arg Ile Lys Glu  
 100 105 110

Asp Arg Pro Ile Thr Ile Lys Asp Asp Lys Gly Asn Leu Asn Arg Cys  
 115 120 125

Ile Ala Asp Val Val Ser Leu Phe Ile Thr Val Met Asp Lys Leu Arg  
 130 135 140

Leu Glu Ile Arg Ala Met Asp Glu Ile Gln Pro Asp Leu Arg Glu Leu  
 145 150 155 160

Met Glu Thr Met His Arg Met Ser His Leu Pro Pro Asp Phe Glu Gly  
 165 170 175

Arg Gln Thr Val Ser Gln Trp Leu Gln Thr Leu Ser Gly Met Ser Ala  
 180 185 190

Ser Asp Glu Leu Asp Asp Ser Gln Val Arg Gln Met Leu Phe Asp Leu  
 195 200 205

Glu Ser Ala Tyr Asn Ala Phe Asn Arg Phe Leu His Ala  
 210 215 220

&lt;210&gt; 284

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 284

Met Gly Asn Ser Gln Val Pro Gln Ser Ser Asp Phe Ser Ser Ile Leu  
 1 5 10 15

Leu Thr Thr Ser Leu Gly Thr Tyr Ser Leu Leu Leu Gly Thr Ala Gly  
 20 25 30

188

Ala Arg Thr Gly Ser Pro Met Ser  
           35                  40

&lt;210&gt; 285

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 285

Met Gln Ala Pro Phe Xaa His Phe Ser Phe Arg Met Phe Ser Asn Leu  
   1                  5                  10                  15

Tyr Cys Phe Ser Asp Phe Gln Pro Asn Ile Ser Pro Cys Pro Leu Cys  
           20                  25                  30

His Cys Ile Leu Pro Xaa His His His Val Phe Leu Leu Leu Ala Val  
           35                  40                  45

Xaa

&lt;210&gt; 286

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (52)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 286

Met Lys Leu Val Thr Met Phe Asp Lys Leu Ser Arg Asn Arg Val Ile  
   1                  5                  10                  15

Gln Pro Met Gly Met Ser Pro Arg Gly His Leu Thr Ser Leu Gln Asp  
           20                  25                  30

Ala Met Cys Glu Thr Met Glu Gln Gln Leu Ser Ser Asp Pro Asp Ser  
           35                  40                  45

189

Asp Pro Asp Xaa  
50

<210> 287  
<211> 32  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (32)  
<223> Xaa equals stop translation

<400> 287  
Met Ala Val Gly Glu Ala Val Phe Val Pro Leu Gln His Pro Pro Leu  
1 5 10 15  
Leu His Gly Ser Pro Ile Pro Lys Leu Leu Pro Gly Pro Leu Leu Xaa  
20 25 30

<210> 288  
<211> 57  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (52)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (57)  
<223> Xaa equals stop translation

<400> 288  
Met Asn Gly Cys His Arg Arg Lys Arg Leu His Leu Cys Lys Thr Ile  
1 5 10 15  
Tyr Leu Leu Trp Phe Val Phe Ser Phe Leu Leu Ser Asn Glu Val Val  
20 25 30  
Ser Ser His Trp His Ile Leu Arg Ala Val Gln Ile Ile Cys Thr Leu  
35 40 45  
Phe His Arg Xaa Ile Ser Ala Phe Xaa  
50 55

<210> 289  
<211> 22  
<212> PRT

190

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 289

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Trp | Val | Ser | Ser | Pro | His | Val | Lys | Arg | Arg | Glu | Cys | Val | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
| Lys | Lys | Pro | Phe | Phe | Xaa |
|     |     |     |     | 20  |     |

&lt;210&gt; 290

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 290

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Phe | Asn | Phe | Phe | Lys | Asn | Pro | Leu | Leu | Thr | Cys | Leu | Phe | Ile | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Tyr | Leu | Tyr | Leu | Ser | Leu | Leu | Val | Asn | Lys | Val | Leu | Phe | Ala | Glu |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gly | Leu | Cys | Cys | Thr | Tyr | Cys | Thr | Thr | Ser | Asn | Thr | Gly | Glu | Gly |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |
|-----|-----|-----|
| Gly | Val | Xaa |
|     |     | 50  |

&lt;210&gt; 291

&lt;211&gt; 98

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 291

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Tyr | Ile | Tyr | His | Ile | Phe | Phe | Ile | His | Ser | Leu | Leu | Asp | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Leu | Gly | Trp | Phe | His | Ile | Phe | Ala | Ile | Val | Ser | Cys | Ala | Ala | Pro |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ile | Ile | Phe | Asn | Ser | Phe | Ala | Phe | Ser | Thr | Tyr | Ile | Ser | Lys | Ser |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Ser | Phe | Tyr | Leu | Gln | Asn | Val | Ser | Cys | Ile | His | Ser | Ser | Leu | Ser |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Phe | Asn | Leu | Phe | Gln | Cys | Pro | Ile | Ile | Ser | Cys | Met | Glu | Glu | Cys |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

191

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 65  |     | 70  |     | 75  |     | 80  |     |     |     |     |     |     |     |     |     |
| Asn | Asn | Trp | Leu | Thr | Gly | Leu | Phe | Leu | His | Phe | Lys | Ile | Lys | Arg | Cys |
|     |     |     |     |     | 85  |     |     |     | 90  |     |     |     |     | 95  |     |

Asp Arg

<210> 292  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

|   |
|---|
| <400> 292   |
| Met Leu Cys Thr Ile Leu Thr Val Val Ile Ile Ile Ala Ala Gln Thr |
| 1 5 10 15   |
| Thr Arg Thr Thr Gly Ile Pro Lys Asn Ala Pro Gly Pro Ala Pro Leu |
| 20 25 30  |

|   |
|---|
| Cys Ala Pro Arg Ser Pro Arg Leu Phe Leu Gln Xaa Tyr Arg Gly Pro |
| 35 40 45  |

|   |
|---|
| Asn Gly Arg Pro Ala His Pro Phe Leu Gly Pro Ser Asp Leu Asp Thr |
| 50 55 60  |

Ser Xaa  
 65

<210> 293  
 <211> 257  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (187)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

<222> (229)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (232)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (236)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (237)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (257)

<223> Xaa equals stop translation

<400> 293

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Leu | Gly | Ala | Lys | Pro | His | Trp | Leu | Pro | Gly | Pro | Leu | His | Ser | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Leu | Pro | Leu | Val | Leu | Val | Leu | Leu | Ala | Leu | Gly | Ala | Gly | Trp | Ala |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Gly | Ser | Glu | Pro | Val | Leu | Leu | Glu | Gly | Glu | Cys | Leu | Val | Val |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Glu | Pro | Gly | Arg | Ala | Ala | Ala | Gly | Gly | Pro | Gly | Gly | Ala | Ala | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Glu | Ala | Pro | Pro | Gly | Arg | Val | Ala | Phe | Xaa | Ala | Val | Arg | Ser | His |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | His | Glu | Pro | Ala | Gly | Glu | Thr | Gly | Asn | Gly | Thr | Ser | Gly | Ala | Ile |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Phe | Asp | Gln | Val | Leu | Val | Asn | Glu | Gly | Gly | Gly | Phe | Asp | Arg | Ala |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Ser | Phe | Val | Ala | Pro | Val | Arg | Gly | Val | Tyr | Ser | Phe | Arg | Phe |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Val | Val | Lys | Val | Tyr | Asn | Arg | Gln | Thr | Val | Gln | Val | Ser | Leu | Met |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asn | Thr | Trp | Pro | Val | Ile | Ser | Ala | Phe | Ala | Asn | Asp | Pro | Asp | Val |
| 145 |     |     |     |     | 150 |     |     |     |     |     | 155 |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Arg | Glu | Ala | Ala | Thr | Ser | Ser | Val | Leu | Leu | Pro | Leu | Asp | Pro | Gly |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Asp | Arg | Val | Ser | Leu | Arg | Leu | Arg | Arg | Gly | Xaa | Ser | Thr | Gly | Trp | Leu |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Glu | Ile | Leu | Lys | Phe | Leu | Trp | Leu | Pro | His | Leu | Pro | Ser | Leu | Lys | Asp |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Pro | Ser | Leu | Ser | Ser | Thr | Arg | Ile | Gln | Pro | Leu | Thr | Thr | Phe | Phe | Cys |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Pro | Leu | Leu | Pro | Xaa | Lys | Gln | Xaa | Lys | Gln | Xaa | Xaa | Xaa | Ser | Leu | Trp |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Leu | Leu | Ser | His | Leu | Phe | Ala | Trp | Glu | Pro | Val | Pro | Asn | Thr | Gln | Val |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |

```
<210> 294
<211> 103
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (78)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<220>
<221> SITE
<222> (80)
<223> Xaa equals any of the naturally occurring L-amino acids

```

```
<220>  
<221> SITE  
<222> (81)  
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>
<221> SITE
<222> (82)
<223> Xaa equals any of the naturally occurring L-amino acids
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```
<220>  
<221> SITE  
<222> (103)  
<223> Xaa equals stop translation
```

```
<400> 294
Met Ala Pro Arg Ala Leu Pro Gly Ser Ala Val Leu Ala Ala Ala Val
  1             5             10            15
```

Phe Val Gly Gly Ala Val Ser Ser Pro Leu Val Ala Pro Asp Asn Gly

194

20                      25                      30  
 Ser Ser Arg Thr Leu His Ser Arg Thr Glu Thr Thr Pro Ser Pro Ser  
                     35                      40                      45  
 Asn Asp Thr Gly Asn Gly His Pro Glu Tyr Ile Ala Tyr Ala Leu Val  
                     50                      55                      60  
 Pro Val Phe Phe Ile Met Gly Leu Phe Gly Val Leu Ile Xaa Pro Xaa  
                     65                      70                      75                      80  
 Xaa Xaa Lys Lys Lys Gly Tyr Arg Cys Thr Thr Glu Ala Glu Gln Asp  
                     85                      90                      95  
 Ile Glu Glu Glu Lys Gly Xaa  
                     100

<210> 295  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (33)  
 <223> Xaa equals stop translation

<400> 295  
 Met Pro Val Thr Leu Ser Ser Leu Gly Phe Trp Val Leu Leu Ser Leu  
                     1                      5                      10                      15  
 Leu Phe Pro Trp Arg Thr Asp Gln Gly Cys Gly Pro Ala Thr Cys Tyr  
                     20                      25                      30

Xaa

<210> 296  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 296  
 Met Val Leu Gly Leu Leu Leu Leu Leu Xaa Phe Phe Ser Phe Ser Ser  
                     1                      5                      10                      15



195

Ser Pro Ser Pro Ser Ser Ser Leu Leu Leu Leu Ser Ser Phe Phe Phe  
                   20                  25                  30

Gln Ser Leu Ala Leu Ser Pro Arg Leu Glu Xaa  
           35                  40

&lt;210&gt; 297

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 297

Glu Trp Leu Val Phe Thr Phe Leu Leu Val Phe Gly Ser Pro Leu Gly  
   1                  5                  10                  15

Lys Gly Pro Leu Xaa  
                   20

&lt;210&gt; 298

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 298

Met Ile Arg Ala Leu Ser Leu Phe Leu Leu Ile Phe Asp Ala Ala Leu  
   1                  5                  10                  15

Phe Ser Leu Ser Val Phe Val Phe Ile Gly His Leu Leu Pro Met Pro  
                   20                  25                  30

Lys Gly Thr Gly Leu His Ser Cys Ala Lys His Leu Ile Lys Ser Leu  
           35                  40                  45

Lys Glu Asn Val Leu Pro Leu Met Asn Tyr Pro Asp Cys Lys Leu Lys  
   50                  55                  60

Ile Asn Ile Ser Pro Xaa  
   65                  70

&lt;210&gt; 299

&lt;211&gt; 75

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

196

&lt;221&gt; SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 299

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Lys | Leu | Ile | Arg | Leu | Ser | Val | Met | Val | Met | Ser | Val | Arg | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Ser | Ile | Tyr | Trp | Val | Leu | Ser | Thr | Val | Pro | Asp | Ala | Val | Gly |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Gly | Gly | Met | Glu | Glu | Glu | Cys | Ser | Arg | Gly | Leu | Cys | Cys | Val |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gly | Gln | His | Lys | Gln | Ala | Lys | Gly | Lys | Arg | Gln | Ala | Trp | Asn | Lys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Glu | Tyr | Gln | Cys | Val | Thr | Tyr | Cys | Xaa |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |

&lt;210&gt; 300

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 300

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Pro | Ala | Leu | Val | Thr | Leu | Leu | Leu | Leu | Phe | Pro | Leu | Leu | Pro | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Ala | Ser | Cys | His | Val | Met | Arg | Cys | Pro | Met | Glu | Arg | Pro | Thr |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

Xaa

&lt;210&gt; 301

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 301

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Ala | Pro | Trp | Gly | Leu | Leu | Lys | Leu | Leu | Leu | Leu | Ala | Val | Phe |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

Xaa

197

<210> 302  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (17)  
 <223> Xaa equals stop translation

<400> 302  
 Met Gln Gln Lys Gln Lys Lys Ala Asn Glu Lys Lys Glu Glu Pro Lys  
           1                  5                  10                  15

Xaa

<210> 303  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (9)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 303  
 Met Gln Ser Pro Lys Phe Leu Ser Xaa Thr Pro Tyr Leu Phe Gln Thr  
           1                  5                  10                  15

Pro Phe His Leu Ile Ser Leu Pro Cys His Phe Phe Ile Phe Lys Met  
                   20                  25                  30

Pro Ile Val Tyr Val Leu Phe Lys Phe Phe Glu Arg Leu Lys Gln Pro  
           35                  40                  45

Leu Ser Lys Ile Pro Phe Cys Leu Leu Ala Phe Lys Phe Ser Ile Arg  
           50                  55                  60

Ala Phe Phe Leu Pro Leu Trp His Ala Ala Leu Trp Leu Ser Phe Val  
           65                  70                  75                  80

Phe Phe Ala Gly Phe Leu His Asp Val Val Val Val Ser Cys Leu Thr  
                   85                  90                  95

Leu Cys Gly Val Val Ser Cys Ser Phe Ser Ser Pro Arg Cys Leu  
           100                  105                  110

<210> 304  
 <211> 12  
 <212> PRT  
 <213> Homo sapiens

198

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 304

Met Ala Leu Leu Ile Ser Ser Leu Ile Trp Ser Xaa  
1 5 10

&lt;210&gt; 305

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 305

Met Gln Met Phe Thr Val Ser Leu Leu Leu Ser Leu Leu Leu Arg Ser  
1 5 10 15

Thr Asp Gln Asn His Leu Gln Leu Leu Val Gly Arg Glu Asp His Tyr  
20 25 30

Gly Gly Xaa  
35

&lt;210&gt; 306

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 306

Met Ser Glu Ser Ala Cys Ile Leu Asn Asn Gln Lys Glu Leu Xaa  
1 5 10 15

&lt;210&gt; 307

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 307

Met Asp Leu Asp Arg Val Lys Ala Glu Ala Thr Glu Asp Ile Thr Ser

199

1                    5                    10                    15  
 Gly Val Leu Cys Leu Leu Phe Leu Arg Leu Pro Pro Asn Ser Cys Ile  
                   20                    25                    30  
 Phe Pro Ser Ala Val Leu Gly Ser Thr Arg Thr Xaa  
                   35                    40

<210> 308  
 <211> 137  
 <212> PRT  
 <213> Homo sapiens

<400> 308  
 Met Met Val Val Gly Thr Gly Thr Ser Leu Ala Leu Ser Ser Leu Leu  
   1                    5                    10                    15  
 Ser Leu Leu Leu Phe Ala Gly Met Gln Met Tyr Ser Arg Gln Leu Ala  
                   20                    25                    30  
 Ser Thr Glu Trp Leu Thr Ile Gln Gly Gly Leu Leu Gly Ser Gly Leu  
                   35                    40                    45  
 Phe Val Phe Ser Leu Thr Ala Phe Asn Asn Leu Glu Asn Leu Val Phe  
                   50                    55                    60  
 Gly Lys Gly Phe Gln Ala Lys Ile Phe Pro Glu Ile Leu Leu Cys Leu  
                   65                    70                    75                    80  
 Leu Leu Ala Leu Phe Ala Ser Gly Leu Ile His Arg Val Cys Val Thr  
                   85                    90                    95  
 Thr Cys Phe Ile Phe Ser Met Val Gly Leu Tyr Tyr Ile Asn Lys Ile  
                   100                    105                    110  
 Ser Ser Thr Leu Tyr Gln Ala Ala Ala Pro Val Leu Thr Pro Ala Lys  
                   115                    120                    125  
 Val Thr Gly Lys Ser Lys Lys Arg Asn  
                   130                    135

<210> 309  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals stop translation

<400> 309  
 Met Phe Ile Phe Leu Phe Leu Cys Val Leu Ser Arg Lys Ile Gln Glu  
   1                    5                    10                    15  
 Glu Tyr Tyr Arg Leu Phe Lys Asn Val Pro Cys Cys Phe Gly Cys Leu

200

20

25

30

Arg Xaa

&lt;210&gt; 310

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (137)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 310

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Thr | Pro | Gly | Pro | Leu | Pro | Val | Leu | Leu | Leu | Leu | Ala | Gly |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Ala | Ala | Arg | Pro | Thr | Pro | Pro | Thr | Cys | Tyr | Ser | Arg | Met | Arg |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Leu | Ser | Gln | Glu | Ile | Thr | Arg | Asp | Phe | Asn | Leu | Leu | Gln | Val | Ser |
|     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Pro | Ser | Glu | Pro | Cys | Val | Arg | Tyr | Leu | Pro | Arg | Leu | Tyr | Leu | Asp |
|     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | His | Asn | Tyr | Cys | Val | Leu | Asp | Lys | Leu | Arg | Asp | Phe | Val | Ala | Ser |
| 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Cys | Trp | Lys | Val | Ala | Gln | Val | Asp | Ser | Leu | Lys | Asp | Lys | Ala |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Lys | Leu | Tyr | Thr | Ile | Met | Asn | Ser | Phe | Cys | Arg | Arg | Asp | Leu | Val |
|     | 100 |     |     |     |     |     | 105 |     |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Leu | Asp | Asp | Cys | Asn | Ala | Leu | Glu | Tyr | Pro | Ile | Pro | Val | Thr |
|     | 115 |     |     |     |     | 120 |     |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Leu | Pro | Asp | Arg | Gln | Arg | Xaa |
| 130 |     |     |     |     |     | 135 |     |     |

&lt;210&gt; 311

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

201

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals stop translation

<400> 311

Met Trp Leu Leu Lys Pro Ser Ala His Ser Pro Val His Xaa Leu Val  
1 5 10 15

Leu Leu Phe Pro Arg Gly Trp Ser Gln Pro Gly Thr His Lys Arg Gln  
20 25 30

Ile Leu Val Asn Xaa Ala Ser Leu Pro Gly Gly Cys Leu Leu Pro Trp  
35 40 45

Ile Trp Ser Gly Ala Ala Leu Arg Phe Xaa  
50 55

<210> 312

<211> 35

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals stop translation

<400> 312

Met Ser Arg Arg Ala Glu Ala Ser Ile Phe Val Leu Pro Lys Thr Leu  
1 5 10 15

Leu Phe Val Leu Phe Pro Ala Phe Pro Ser Pro Ala Val Gly Cys Pro  
20 25 30

Val Pro Xaa  
35

<210> 313

<211> 90

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 313

Met Ala Leu Glu Met Val Trp Gly Ser Val Tyr His Cys Ser Cys Tyr  
1 5 10 15

Ile Thr Pro Trp Ser Lys Ile Gln Ser Phe Ser Leu Ser Leu Phe Gln  
20 25 30

202

Phe Ile Leu Gln Glu Val Asn Ile Thr Leu Pro Glu Asn Ser Val Trp  
 35 40 45

Tyr Glu Arg Tyr Lys Phe Asp Ile Pro Val Phe His Leu Asn Gly Gln  
 50 55 60

Phe Leu Met Met His Arg Val Asn Thr Ser Lys Leu Glu Lys Gln Leu  
 65 70 75 80

Leu Lys Leu Glu Gln Gln Ser Thr Gly Xaa  
 85 90

<210> 314

<211> 95

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (95)

<223> Xaa equals stop translation

<400> 314

Met Phe Val Leu Phe Ser Leu Pro Lys Tyr Ala Gly Leu Arg Leu Pro  
 1 5 10 15

Ile Pro Gly Leu Ser Ala Leu Leu Val Phe Leu Leu Ser Leu Phe Ser  
 20 25 30

Arg Arg Ala Gln Val Glu Leu Thr Thr Gly Arg Glu Thr Leu Pro Lys  
 35 40 45

Asn Leu Gln Gly Tyr Phe Pro Glu Phe Gly Phe Gln Val Gln Asn Phe  
 50 55 60

Leu Ser Cys Lys Ile Tyr Ala Ala Ser Gln Lys Gln Pro Leu Pro Pro  
 65 70 75 80

Leu Tyr Gln Leu Arg Phe Tyr Leu Lys His Met Gly Leu Pro Xaa  
 85 90 95

<210> 315

<211> 44

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> Xaa equals stop translation

<400> 315

Met Ser Ser His Trp Thr Leu Lys Ile Leu Leu Val Pro Leu Phe Tyr  
 1 5 10 15



203

Leu Ser Leu Glu Phe Pro Ser Gly Phe Val Leu Cys Leu Ala Asn Asp  
                   20                  25                  30

Leu Gly Tyr His Phe Ser Ser Arg Val Arg Ser Xaa  
                   35                  40

&lt;210&gt; 316

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 316

Met Leu Val Val Asn Ile Asn Leu Val Phe Leu Leu Phe Phe Ile Phe  
   1                  5                  10                  15

Leu Cys Tyr Leu Asp Ala Cys Ile Asn Val Phe Cys Phe Tyr Xaa  
                   20                  25                  30

&lt;210&gt; 317

&lt;211&gt; 113

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (113)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 317

Met Pro Val Leu Pro Gly Arg Thr Thr Ala Leu Leu Ser Leu Thr Leu  
   1                  5                  10                  15

Ala Phe Ala Val Pro Cys Ser Gly Val Glu Ala Gly Pro Cys Val Pro  
                   20                  25                  30

Arg Ser His Gly Cys Ser Ser Trp Glu Ala Ser Val Cys Val Thr Ser  
                   35                  40                  45

Ser Thr Pro Gly Gly Ser Trp Arg Ala Arg Ala Leu Phe Pro Ser Ala  
                   50                  55                  60

Ala Trp His Arg Xaa Ala Ala Trp Asp Ser Pro Trp Thr Gln Thr Gly  
   65                  70                  75                  80

Asp Phe Ala Arg Gly Ala Met Gly Gly Ala Gly Ala Leu Pro Gly Gly  
                   85                  90                  95

204

Cys Val Cys Ile Ser Gly Arg Pro Arg Ala Gln Lys Leu Pro Ala Leu  
 100 105 110

Xaa

&lt;210&gt; 318

&lt;211&gt; 235

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 318

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro  
 1 5 10 15

Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser  
 20 25 30

Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro  
 35 40 45

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln  
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro  
 65 70 75 80

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro  
 85 90 95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly  
 100 105 110

Asn Tyr Val Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr Pro Ile  
 115 120 125

Met Pro Ser Pro Ala Asp Ser Thr Asn Ser Gly Asp Asn Met Tyr Thr  
 130 135 140

Leu Met Asn Ala Val Pro Pro Gly Pro Asn Arg Pro Asn Phe Pro Met  
 145 150 155 160

Gly Pro Gly Ser Asp Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser  
 165 170 175

His His Met Asn Gly Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser  
 180 185 190

Lys Asn Ser Pro Asn Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro  
 195 200 205

Arg Asp Asp Gly Glu Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser  
 210 215 220

Glu Ser Tyr Ser Pro Ser Met Thr Met Ser Val  
 225 230 235

205

<210> 319  
<211> 35  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (35)  
<223> Xaa equals stop translation

<400> 319  
Met Glu Asn Phe Phe Phe Ser Phe Tyr Leu Phe Leu Ile Thr Leu Ile  
1 5 10 15  
Pro Asn Gly Arg Thr Leu Ser Thr Thr Ala Asp His Cys Lys Ile Pro  
20 25 30  
Cys Ile Xaa  
35

<210> 320  
<211> 35  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (35)  
<223> Xaa equals stop translation

<400> 320  
Met Glu Leu Trp Glu Leu Ala Leu Cys Leu Leu Val Ala Leu Ser Ala  
1 5 10 15  
His Met Phe Thr Val Gln Leu Leu Ala Asp Leu Gly Phe Leu Phe Gly  
20 25 30  
Gly Phe Xaa  
35

<210> 321  
<211> 82  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (82)  
<223> Xaa equals stop translation

<400> 321  
Met Gly Ala Gly Ile Leu Ala Leu Leu Leu Pro Leu Glu Ser Val Leu  
1 5 10 15

206

Thr Cys Ser Trp Ile Ser Val Ser Thr Ser Glu Arg Gln Leu Trp Gln  
                   20                  25                  30  
 Ser Ser Gln Lys Ala Thr Ile Leu Ser Leu Lys Leu Asp Ser Cys Phe  
                   35                  40                  45  
 Cys Gly His Ser Gly Leu Lys Gly Lys Asn Glu Asp Thr Asp Ser Ser  
           50                  55                  60  
 Val Pro Ile Ile Pro Ser Lys Thr His Thr His Leu Gly Lys His Leu  
   65                  70                  75                  80  
 Ile Xaa

&lt;210&gt; 322

&lt;211&gt; 72

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 322

Met Phe Tyr Phe Val Leu Phe Ile Tyr Ser Ser Ser Glu Thr Trp Ser  
   1                  5                  10                  15

Gly Ser Val Ala Gln Asp Gly Val His Gly Val Ile Ile Gly His Cys  
                   20                  25                  30

Ser Val Glu Leu Pro Gly Ser Gly Asp Pro Pro Ala Ser Ala Xaa Leu  
           35                  40                  45

Val Ala Gly Thr Ile Gly Thr Cys Pro Thr Met Pro Gly Phe Val Tyr  
   50                  55                  60

Phe Leu Asn Asp Val Xaa Asn Xaa  
   65                  70

&lt;210&gt; 323

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

207

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals stop translation

<400> 323  
 Met Asp Ser Thr Leu Arg Gln Gly Arg Xaa Leu Leu Thr Leu Val Pro  
 1 5 10 15

Ala Ser Leu Phe Ser Leu Thr Leu Gly Gly Pro Gly Pro Trp Lys Asp  
 20 25 30

Pro Xaa

<210> 324  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (111)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (112)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (115)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 324  
 Met Gln Val Val Gly Ser Trp Pro Gly Arg Val Gly Val Val Gly Leu  
 1 5 10 15

Ala Phe Ser Leu Val Ile Pro Pro Pro Ala Ile Cys Ile Ala Gly Pro  
 20 25 30

Ala Pro Gly Leu Gly Gly Gly Glu Arg Gln Gln Lys Gly Leu Gly Arg  
 35 40 45

Gly Gly Gly Gly Leu Arg Asn Cys Pro Gly Arg Val Gly Met Ala Ala  
 50 55 60

Glu Pro Gly Ala Leu Leu Cys Leu Thr Ser Arg Asp Gly Ser Leu Leu  
 65 70 75 80

Leu Ser Cys Val Arg Pro His His Val Ile Lys Pro Lys Gly Thr Ala

208

|   |     |     |    |
|---|-----|-----|----|
|   | 85  | 90  | 95 |
| Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Xaa Xaa |     |     |    |
| 100   | 105 | 110 |    |

|             |
|-------------|
| Gly Gly Xaa |
| 115         |

<210> 325  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (98)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (99)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (100)  
 <223> Xaa equals any of the naturally occurring L-amino acids

|   |
|---|
| <400> 325   |
| Met Asp Leu Pro Gln Phe Ile Tyr Leu Phe Ile Phe Cys Phe Cys Cys |
| 1 5 10 15   |

|   |
|---|
| Leu Ala Ile Val Asn Asn Ala Ser Ile Asn Ile His Ile Gln Val Ser |
| 20 25 30  |

|   |
|---|
| Met Trp Leu Tyr Val Phe Ile Ser Leu Gly Tyr Leu His Gly Ser Arg |
| 35 40 45  |

|   |
|---|
| Ile Leu Gly His Asn Ile Ile Leu Cys Leu Thr Ser Gln Arg Ile Ala |
| 50 55 60  |

|   |
|---|
| Lys Arg Phe Phe Ile Val Ala Ala Ser Phe Thr Phe Pro Pro Ala Met |
| 65 70 75 80   |

|   |
|---|
| Tyr Lys Asp Phe Tyr Phe Ser Ile Ser Leu His Leu Pro Thr Leu Leu |
| 85 90 95  |

|   |
|---|
| Phe Xaa Xaa Xaa Phe Val Phe Ser Leu Leu Pro Pro |
| 100 105   |

<210> 326  
 <211> 65  
 <212> PRT  
 <213> Homo sapiens

<220>

209

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 326

Met Cys Ser Pro Ser Leu Ser Ser Ser Pro Pro Pro Leu Leu Gln Val  
 1 5 10 15

Phe Phe Phe Phe Phe Phe Ser Pro His Trp Ala Ala Lys Val Val Pro  
 20 25 30

Gln Trp Lys Xaa Arg His Pro Gln Val Ser Ser Gln Leu Leu Leu Cys  
 35 40 45

Phe Leu Arg Val Asn Cys Gln Phe Leu Phe Leu Gln Glu Ile Leu Phe  
 50 55 60

Xaa

65

&lt;210&gt; 327

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

Met Cys Leu Ser Arg Trp Lys Ile Phe Tyr Thr Leu Leu Ile Leu Phe  
 1 5 10 15

Ala Phe Phe Ser Ile Thr Ser Glu Asn Glu Thr Phe Tyr Met Ile Ile  
 20 25 30

Ile His His Asn Pro Thr Gln Ile Thr Ala Ser Cys Ser Phe Thr Phe  
 35 40 45

Leu

&lt;210&gt; 328

&lt;211&gt; 293

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 328

Met Glu Arg Pro Asp Trp Glu Thr Ala Ile Gln Lys Pro Leu Cys Ser  
 1 5 10 15

210

Leu Pro Ala Gly Ser Gly Asn Ala Leu Ala Ala Ser Leu Asn His Tyr  
 20 25 30  
 Ala Gly Tyr Xaa Gln Val Thr Asn Glu Asp Leu Leu Thr Asn Cys Thr  
 35 40 45  
 Leu Leu Leu Cys Arg Arg Leu Ser Pro Met Asn Leu Leu Ser Leu  
 50 55 60  
 His Thr Ala Ser Gly Leu Arg Leu Phe Ser Val Leu Ser Leu Ala Trp  
 65 70 75 80  
 Gly Phe Ile Ala Asp Val Asp Leu Glu Ser Glu Lys Tyr Arg Arg Leu  
 85 90 95  
 Gly Glu Met Arg Phe Thr Leu Gly Thr Phe Leu Arg Leu Ala Ala Leu  
 100 105 110  
 Arg Thr Tyr Arg Gly Arg Leu Ala Tyr Leu Pro Val Gly Arg Val Gly  
 115 120 125  
 Ser Lys Thr Pro Ala Ser Pro Val Val Val Gln Gln Gly Pro Val Asp  
 130 135 140  
 Ala His Leu Val Pro Leu Glu Glu Pro Val Pro Ser His Trp Thr Val  
 145 150 155 160  
 Val Pro Asp Glu Asp Phe Val Leu Val Leu Ala Leu Leu His Ser His  
 165 170 175  
 Leu Gly Ser Glu Met Phe Ala Ala Pro Met Gly Arg Cys Ala Ala Gly  
 180 185 190  
 Val Met His Leu Phe Tyr Val Arg Ala Gly Val Ser Arg Ala Met Leu  
 195 200 205  
 Leu Arg Leu Phe Leu Ala Met Glu Lys Gly Arg His Met Glu Tyr Glu  
 210 215 220  
 Cys Pro Tyr Leu Val Tyr Val Pro Val Val Ala Phe Arg Leu Glu Pro  
 225 230 235 240  
 Lys Asp Gly Lys Gly Val Phe Ala Val Asp Gly Glu Leu Met Val Ser  
 245 250 255  
 Glu Ala Val Gln Gly Gln Val His Pro Asn Tyr Phe Trp Met Val Ser  
 260 265 270  
 Gly Cys Val Glu Pro Pro Pro Ser Trp Lys Pro Gln Gln Met Pro Pro  
 275 280 285  
 Pro Glu Glu Pro Leu  
 290

&lt;210&gt; 329

&lt;211&gt; 68



211

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 329

Met Pro Leu Glu Gly Phe Cys Leu Val Leu Asp Ile Gly Phe Leu Leu  
 1 5 10 15

Val Met Leu Ile Ser Leu Ala Ser Glu Cys Phe Thr Thr Cys Leu Asp  
 20 25 30

Ser Phe Ser Thr Thr Glu Pro Gly Cys Lys Phe Tyr Lys Leu Leu His  
 35 40 45

Ser Val Ser Leu Leu Asn Ile Asn Phe Asn Val Lys Ser Leu Leu Cys  
 50 55 60

Ser His Ile Xaa  
 65

&lt;210&gt; 330

&lt;211&gt; 105

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (105)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 330

Met Pro Leu Gln Leu Ser Gly Gln Tyr Trp Ile Ser Leu Leu Val Phe  
 1 5 10 15

Leu Ser Leu Gln Pro Phe Pro Gln Ala Ala Ile Pro Cys Ala Leu Thr  
 20 25 30

Asp Val Gly Gly Ser Cys Val Ile Cys His Ile Leu Leu Asn Cys Leu  
 35 40 45

Cys Ile Leu Phe Thr Leu Thr Ala Pro Ser Leu Ser His Val Leu Leu  
 50 55 60

Ile Lys Met Ser Leu Ser Val Cys Tyr Glu Pro Gly Ala Asp Leu Ser  
 65 70 75 80

Asp Arg Ala Ala Thr Gly Asn Lys Lys Leu Thr Arg Ser Thr Cys Leu  
 85 90 95

Leu Met His Ser Asn Lys Leu Cys Xaa  
 100 105

212

<210> 331  
<211> 58  
<212> PRT  
<213> Homo sapiens

<400> 331  
Met Trp Gly Cys Ser Gly Leu Gly His Arg Thr Val Ser Phe Leu Leu  
1 5 10 15  
Leu Leu Pro Cys Ser Phe Pro Arg Pro Cys Gly Leu Phe Gly Leu Ile  
20 25 30  
Pro Ile Ser Arg Pro Cys Lys Val Glu Ala Pro Arg Pro Leu Ser Pro  
35 40 45  
Thr Thr Leu Met Cys Gln Ser Pro Leu Leu  
50 55

<210> 332  
<211> 39  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (14)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (39)  
<223> Xaa equals stop translation

<400> 332  
Met Leu Asn Val Leu Ser Lys Val Gln Gln Leu Val Ser Xaa Leu Gly  
1 5 10 15  
Leu Val Thr Phe Leu Leu Asn His Ser Ala Ala Gly Gly Ser Pro Gln  
20 25 30  
His Arg Trp Leu Leu Leu Xaa  
35

<210> 333  
<211> 72  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (58)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (72)

213

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 333

Met Lys Ala Ile Ala Arg Ala Cys Leu Leu Leu Ser Leu Leu Val Leu  
 1 5 10 15

Pro His Val Val Ser Glu His Leu Phe Trp His His Asn Pro Arg His  
 20 25 30

Pro Val Ile Trp Pro Phe Pro Pro Phe His Leu Ile Ser Cys Ser Val  
 35 40 45

Ser Ala Ser Thr Trp His Leu Gly Glu Xaa Leu Leu Leu Val Pro  
 50 55 60

Ile Ala Pro Ser Val Trp Ser Xaa  
 65 70

&lt;210&gt; 334

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (62)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 334

Met Glu Gln Gly Gly Gly Pro Arg Leu Leu Leu Ile Pro Gly Leu  
 1 5 10 15

Leu His Asn Thr Tyr Leu Ala Arg Pro Gly Asp Phe Pro Ala Gln Gly  
 20 25 30

Thr Thr Glu Asn Thr Glu Cys Gln Gly Ser Pro Ser Pro Ile Ser His  
 35 40 45

Leu Gly Lys Val Arg Ser Leu Asp Ser Asn Thr Gln Ile Xaa  
 50 55 60

&lt;210&gt; 335

&lt;211&gt; 286

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (286)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 335

Met Pro Leu Leu Phe Phe Ser Val Ser Thr Leu Phe Ser Gly Ser Val  
 1 5 10 15

Thr Leu Gln Gln Arg Gly Met Phe Leu Pro Trp Thr Gly Thr Gly Glu

214

| 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Val | Leu | Ala | Leu | Leu | Trp | Pro | Arg | Phe | Glu | Leu | Ile | Leu | Glu | Met |
|     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Asn | Val | Gln | Ser | Val | Arg | Ser | Thr | Asp | Pro | Gln | Arg | Leu | Gly | Gly | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Asp | Thr | Arg | Pro | His | Tyr | Ile | Thr | Arg | Arg | Tyr | Ala | Glu | Phe | Ser | Ser |
|     | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |
| Ala | Leu | Val | Ser | Ile | Asn | Gln | Thr | Ile | Pro | Asn | Glu | Arg | Thr | Met | Gln |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Leu | Leu | Gly | Gln | Leu | Gln | Val | Glu | Val | Glu | Asn | Phe | Val | Leu | Arg | Val |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |     |
| Ala | Ala | Glu | Phe | Ser | Ser | Arg | Lys | Glu | Gln | Leu | Val | Phe | Leu | Ile | Asn |
|     | 115 |     |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Asn | Tyr | Asp | Met | Met | Leu | Gly | Val | Leu | Met | Glu | Arg | Ala | Ala | Asp | Asp |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Ser | Lys | Glu | Val | Glu | Ser | Phe | Gln | Gln | Leu | Leu | Asn | Ala | Arg | Thr | Gln |
|     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |
| Glu | Phe | Ile | Glu | Glu | Leu | Leu | Ser | Pro | Pro | Phe | Gly | Gly | Leu | Val | Ala |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Phe | Val | Lys | Glu | Ala | Glu | Ala | Leu | Ile | Glu | Arg | Gly | Gln | Ala | Glu | Arg |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Leu | Arg | Gly | Glu | Glu | Ala | Arg | Val | Thr | Gln | Leu | Ile | Arg | Gly | Phe | Gly |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ser | Ser | Trp | Lys | Ser | Ser | Val | Glu | Ser | Leu | Ser | Gln | Asp | Val | Met | Arg |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Ser | Phe | Thr | Asn | Phe | Arg | Asn | Gly | Thr | Ser | Ile | Ile | Gln | Gly | Ala | Leu |
|     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     | 240 |
| Thr | Gln | Leu | Ile | Gln | Leu | Tyr | His | Arg | Phe | His | Arg | Val | Leu | Ser | Gln |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     | 255 |     |
| Pro | Gln | Leu | Arg | Ala | Leu | Pro | Ala | Arg | Ala | Glu | Leu | Ile | Asn | Ile | His |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| His | Leu | Met | Val | Glu | Leu | Lys | Lys | His | Lys | Pro | Asn | Phe | Xaa |     |     |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |

&lt;210&gt; 336

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

215

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 336

Met Phe Arg Ala Leu Arg Asp Leu Leu Thr His Tyr Pro Gln Gln Ile  
 1 5 10 15

Leu Leu Gln Val Leu Val Val Met Tyr Gln Val Leu Gln Val Trp Glu  
 20 25 30

Leu Pro Trp Pro Glu Leu Ile His Leu Gln Gly Ile Val Pro Thr Asp  
 35 40 45

Gln Leu His Leu Lys Gln Xaa  
 50 55

&lt;210&gt; 337

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 337

Met Ser Tyr Pro Leu Phe Leu Phe Met Ser Cys Met Val Ile Ser Leu  
 1 5 10 15

Ser Pro Asn Ala Gly Ser Gln Thr Ser Thr Val Arg Cys Leu Ser Asp  
 20 25 30

Leu Val Thr Phe Thr Leu Ile Lys Gly Ser Pro Val His Gln Thr Pro  
 35 40 45

Tyr Leu Glu Ser Ser Ile Asn Cys Ile Thr Phe  
 50 55

&lt;210&gt; 338

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (120)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 338

Met His Pro Ala Arg Lys Leu Leu Ser Leu Leu Phe Leu Ile Leu Met  
 1 5 10 15

Gly Thr Glu Leu Thr Gln Asp Ser Ala Ala Pro Asp Ser Leu Leu Arg  
 20 25 30

Ser Ser Lys Gly Ser Thr Arg Gly Ser Leu Ala Ala Ile Val Ile Trp  
 35 40 45

Arg Gly Lys Ser Glu Ser Arg Ile Ala Lys Thr Pro Gly Ile Phe Arg  
 50 55 60

216

Gly Gly Gly Thr Leu Val Leu Pro Pro Thr His Thr Pro Glu Trp Leu  
65 70 75 80

Ile Leu Pro Leu Gly Ile Thr Leu Pro Leu Gly Ala Pro Glu Thr Gly  
85 90 95

Gly Gly Asp Cys Ala Ala Glu Thr Trp Lys Gly Ser Gln Arg Ala Gly  
100 105 110

Gln Leu Cys Ala Leu Leu Ala Xaa  
115 120

<210> 339

<211> 38

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 339

Met Pro Ser Phe Phe Leu Ser Leu Ile Gln Thr Asn Thr Leu Gly Ser  
1 5 10 15

Ala Ser Phe Leu Phe Leu Thr Leu His Ile His Leu Ser Pro Asn  
20 25 30

Xaa Val His Ser Ala Ser  
35

<210> 340

<211> 46

<212> PRT

<213> Homo sapiens

<400> 340

Met Phe Ser Arg Thr Ser Asn Phe Trp Thr Phe Phe Phe Gln Phe Leu  
1 5 10 15

Ile Phe Lys Val Phe Leu Val Leu Lys Asn Leu Phe Thr Ser Gln Lys  
20 25 30

Ile Tyr Lys Ile Tyr Ser Glu Lys Pro Lys Lys Lys Lys Lys  
35 40 45

<210> 341

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

217

&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (62)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 341

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Ser | Leu | Leu | Ser | Ala | Gly | Leu | Gln | Ala | Ser | Leu | Cys | Gly | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Leu | Trp | Ala | Ser | Thr | Trp | Tyr | Leu | Val | Cys | Cys | Leu | Leu | Pro | Phe |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | His | Gln | Gly | Cys | Cys | Asp | His | Lys | Ser | Lys | Gln | Gln | Tyr | Ile | Pro |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Leu | Lys | Ser | Tyr | Cys | Gly | Leu | Ser | Thr | Ile | Glu | Ile | Xaa |
|     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |

&lt;210&gt; 342

&lt;211&gt; 87

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 342

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Leu | Phe | Cys | Phe | Val | Leu | Phe | Cys | Phe | Val | Phe | Glu | Met | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Ser | Val | Thr | Gln | Ala | Gly | Val | Gln | Trp | Cys | Asp | Leu | Gly | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gln | Ala | Pro | Pro | Pro | Gly | Phe | Ser | Pro | Phe | Ser | Cys | Leu | Ser | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ser | Ser | Trp | Asp | Tyr | Arg | Arg | Pro | Pro | Pro | Arg | Pro | Ala | Asn | Phe |
|     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Tyr | Phe | Leu | Val | Glu | Thr | Gly | Phe | His | His | Val | Ser | Gln | Asp | Gly |
|     | 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asp | Leu | Leu | Thr | Ser | Xaa |
|     |     |     |     | 85  |     |     |

&lt;210&gt; 343

&lt;211&gt; 538

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

218

&lt;221&gt; SITE

&lt;222&gt; (538)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 343

Met Ser Thr Lys Lys Leu Cys Ile Val Gly Gly Ile Leu Leu Val Phe  
 1 5 10 15

Gln Ile Ile Ala Phe Leu Val Gly Gly Leu Ile Ala Pro Gly Pro Thr  
 20 25 30

Thr Ala Val Ser Tyr Met Ser Val Lys Cys Val Asp Ala Arg Lys Asn  
 35 40 45

His His Lys Thr Lys Trp Phe Val Pro Trp Gly Pro Asn His Cys Asp  
 50 55 60

Lys Ile Arg Asp Ile Glu Glu Ala Ile Pro Arg Glu Ile Glu Ala Asn  
 65 70 75 80

Asp Ile Val Phe Ser Val His Ile Pro Leu Pro His Met Glu Met Ser  
 85 90 95

Pro Trp Phe Gln Phe Met Leu Phe Ile Leu Gln Leu Asp Ile Ala Phe  
 100 105 110

Lys Leu Asn Asn Gln Ile Arg Glu Asn Ala Glu Val Ser Met Asp Val  
 115 120 125

Ser Leu Ala Tyr Arg Asp Asp Ala Phe Ala Glu Trp Thr Glu Met Ala  
 130 135 140

His Glu Arg Val Pro Arg Lys Leu Lys Cys Thr Phe Thr Ser Pro Lys  
 145 150 155 160

Thr Pro Glu His Glu Gly Arg Tyr Tyr Glu Cys Asp Val Leu Pro Phe  
 165 170 175

Met Glu Ile Gly Ser Val Ala His Lys Phe Tyr Leu Leu Asn Ile Arg  
 180 185 190

Leu Pro Val Asn Glu Lys Lys Lys Ile Asn Val Gly Ile Gly Glu Ile  
 195 200 205

Lys Asp Ile Arg Leu Val Gly Ile His Gln Asn Gly Gly Phe Thr Lys  
 210 215 220

Val Trp Phe Ala Met Lys Thr Phe Leu Thr Pro Ser Ile Phe Ile Ile  
 225 230 235 240

Met Val Trp Tyr Trp Arg Arg Ile Thr Met Met Ser Arg Pro Pro Val  
 245 250 255

Leu Leu Glu Lys Val Ile Phe Ala Leu Gly Ile Ser Met Thr Phe Ile  
 260 265 270

Asn Ile Pro Val Glu Trp Phe Ser Ile Gly Phe Asp Trp Thr Trp Met  
 275 280 285



219

Leu Leu Phe Gly Asp Ile Arg Gln Gly Ile Phe Tyr Ala Met Leu Leu  
 290 295 300  
 Ser Phe Trp Ile Ile Phe Cys Gly Glu His Met Met Asp Gln His Glu  
 305 310 315 320  
 Arg Asn His Ile Ala Gly Tyr Trp Lys Gln Val Gly Pro Ile Ala Val  
 325 330 335  
 Gly Ser Phe Cys Leu Phe Ile Phe Asp Met Cys Glu Arg Gly Val Gln  
 340 345 350  
 Leu Thr Asn Pro Phe Tyr Ser Ile Trp Thr Thr Asp Ile Gly Thr Glu  
 355 360 365  
 Leu Ala Met Ala Phe Ile Ile Val Ala Gly Ile Cys Leu Cys Leu Tyr  
 370 375 380  
 Phe Leu Phe Leu Cys Phe Met Val Phe Gln Val Phe Arg Asn Ile Ser  
 385 390 395 400  
 Gly Lys Gln Ser Ser Leu Pro Ala Met Ser Lys Val Arg Arg Leu His  
 405 410 415  
 Tyr Glu Gly Leu Ile Phe Arg Phe Lys Phe Leu Met Leu Ile Thr Leu  
 420 425 430  
 Ala Cys Ala Ala Met Thr Val Ile Phe Phe Ile Val Ser Gln Val Thr  
 435 440 445  
 Glu Gly His Trp Lys Trp Gly Gly Val Thr Val Gln Val Asn Ser Ala  
 450 455 460  
 Phe Phe Thr Gly Ile Tyr Gly Met Trp Asn Leu Tyr Val Phe Ala Leu  
 465 470 475 480  
 Met Phe Leu Tyr Ala Pro Ser His Lys Asn Tyr Gly Glu Asp Gln Ser  
 485 490 495  
 Asn Gly Met Gln Leu Pro Cys Lys Ser Arg Glu Asp Cys Ala Leu Phe  
 500 505 510  
 Val Ser Glu Leu Tyr Gln Glu Leu Phe Ser Ala Ser Lys Tyr Ser Phe  
 515 520 525  
 Ile Asn Asp Asn Ala Ala Ser Gly Ile Xaa  
 530 535

&lt;210&gt; 344

&lt;211&gt; 202

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (202)

220

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 344

Met Gly Ile Ala Leu Ala Val Leu Gly Trp Leu Ala Val Met Leu Cys  
 1 5 10 15

Cys Ala Leu Pro Met Trp Arg Val Thr Ala Phe Ile Gly Ser Asn Ile  
 20 25 30

Val Thr Ser Gln Thr Ile Trp Glu Gly Leu Trp Met Asn Cys Val Val  
 35 40 45

Gln Ser Thr Gly Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala  
 50 55 60

Leu Pro Gln Asp Leu Gln Ala Ala Arg Ala Leu Val Ile Ile Ser Ile  
 65 70 75 80

Ile Val Ala Ala Leu Gly Val Leu Leu Ser Val Val Gly Gly Lys Cys  
 85 90 95

Thr Asn Cys Leu Glu Asp Glu Ser Ala Lys Ala Lys Thr Met Ile Val  
 100 105 110

Ala Gly Val Val Phe Leu Leu Ala Gly Leu Met Val Ile Val Pro Val  
 115 120 125

Ser Trp Thr Ala His Asn Ile Ile Gln Asp Phe Tyr Asn Pro Leu Val  
 130 135 140

Ala Ser Gly Gln Lys Arg Glu Met Gly Ala Ser Leu Tyr Val Gly Trp  
 145 150 155 160

Ala Ala Ser Gly Leu Leu Leu Leu Gly Gly Gly Leu Leu Cys Cys Asn  
 165 170 175

Cys Pro Pro Arg Thr Asp Lys Pro Tyr Ser Ala Lys Tyr Ser Ala Ala  
 180 185 190

Arg Ser Ala Ala Ala Ser Asn Tyr Val Xaa  
 195 200

&lt;210&gt; 345

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 345

Met Val Ser Ile Ser Val Val Leu Arg Val Ser Leu Pro Thr Leu Glu  
 1 5 10 15

Pro Val Pro Val Ala Gly Arg Ser Ile Trp Ile Ser Thr Thr Ser Pro  
 20 25 30

Ser Met Ile Ser Val Ser Ser Leu Met Arg Thr Pro Met Asp Arg Arg  
 35 40 45

221

Lys Ala Cys Val Ser Ala Ser Val Leu Leu Ile Ser Arg Glu Lys Ile  
 50 55 60

Ser Leu Pro Ala Met Ala Val Asn Gly Val Ser Gly Pro Arg Ala Cys  
 65 70 75 80

Ala Met Pro Met Ala Met Ala Val Phe Pro Val Pro Gly Trp Pro Ala  
 85 90 95

Ile Arg Thr Ala Arg Pro Ala Ile Phe Pro Ser Arg Ile Ile Ser Ser  
 100 105 110

Thr Thr Pro Ala Ala Arg Arg Ala Ala Ser  
 115 120

&lt;210&gt; 346

&lt;211&gt; 260

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 346

Met Leu Ala Leu Leu Gly Leu Ser Gln Ala Leu Asn Ile Leu Leu Gly  
 1 5 10 15

Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys Glu Lys Gly  
 20 25 30

Asn Phe Asn Val Ala His Gly Leu Ala Trp Ser Tyr Tyr Ile Gly Tyr  
 35 40 45

Leu Arg Leu Ile Leu Pro Glu Leu Gln Ala Arg Ile Arg Thr Tyr Asn  
 50 55 60

Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln Arg Leu Tyr  
 65 70 75 80

Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met Ala  
 85 90 95

Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly Asp  
 100 105 110

Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn Ser Ile Tyr Glu Leu  
 115 120 125

Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val Leu Glu Tyr Ala Thr  
 130 135 140

Pro Leu Gln Thr Leu Phe Ala Met Ser Gln Tyr Ser Gln Ala Gly Phe  
 145 150 155 160

Ser Gly Glu Asp Arg Leu Glu Gln Ala Lys Leu Phe Cys Arg Thr Leu  
 165 170 175

Glu Asp Ile Leu Ala Asp Ala Pro Glu Ser Gln Asn Asn Cys Arg Leu  
 180 185 190

222

Ile Ala Tyr Gln Glu Pro Ala Asp Asp Ser Ser Phe Ser Leu Ser Gln  
 195 200 205

Glu Val Leu Arg His Leu Arg Gln Glu Glu Lys Glu Glu Val Thr Val  
 210 215 220

Gly Ser Leu Lys Thr Ser Ala Val Pro Ser Thr Ser Thr Met Ser Gln  
 225 230 235 240

Glu Pro Glu Leu Leu Ile Ser Gly Met Glu Lys Pro Leu Pro Leu Arg  
 245 250 255

Thr Asp Phe Ser  
 260

&lt;210&gt; 347

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 347

Met Thr Pro Gln Lys Pro Ala Leu Ala Val Leu Leu Leu Glu Val Pro  
 1 5 10 15

Leu Leu Leu Thr Leu Ser Val Leu Lys Lys Arg Cys Leu Val Thr Cys  
 20 25 30

Glu Pro Thr Ser Arg Phe Val Ser Cys Asp Leu Pro Leu Ser Val Xaa  
 35 40 45

&lt;210&gt; 348

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (288)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (334)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 348

Met Ala Ala Ala Ala Trp Leu Gln Val Leu Pro Val Ile Leu Leu Leu  
 1 5 10 15

223

Leu Gly Ala His Pro Ser Pro Leu Ser Phe Phe Ser Ala Gly Pro Ala  
                   20                  25                  30

Thr Val Ala Ala Ala Asp Arg Ser Lys Trp His Ile Pro Ile Pro Ser  
                   35                  40                  45

Gly Lys Asn Tyr Phe Ser Phe Gly Lys Ile Leu Phe Arg Asn Thr Thr  
                   50                  55                  60

Ile Phe Leu Lys Phe Asp Gly Glu Pro Cys Asp Leu Ser Leu Asn Ile  
                   65                  70                  75                  80

Thr Trp Tyr Leu Lys Ser Ala Asp Cys Tyr Asn Glu Ile Tyr Asn Phe  
                   85                  90                  95

Lys Ala Glu Glu Val Glu Leu Tyr Leu Glu Lys Leu Lys Glu Lys Arg  
                   100                  105                  110

Gly Leu Ser Gly Lys Tyr Gln Thr Ser Ser Lys Leu Phe Gln Asn Cys  
                   115                  120                  125

Ser Glu Leu Phe Lys Thr Gln Thr Phe Ser Gly Asp Phe Met His Arg  
                   130                  135                  140

Leu Pro Leu Leu Gly Glu Lys Gln Glu Ala Lys Glu Asn Gly Thr Asn  
                   145                  150                  155                  160

Leu Thr Phe Ile Gly Asp Lys Thr Ala Met His Glu Pro Leu Gln Thr  
                   165                  170                  175

Trp Gln Asp Ala Pro Tyr Ile Phe Ile Val His Ile Gly Ile Ser Ser  
                   180                  185                  190

Ser Lys Glu Ser Ser Lys Glu Asn Ser Leu Ser Asn Leu Phe Thr Met  
                   195                  200                  205

Thr Val Glu Val Lys Gly Pro Tyr Glu Tyr Leu Thr Leu Glu Asp Tyr  
                   210                  215                  220

Pro Leu Met Ile Phe Phe Met Val Met Cys Ile Val Tyr Val Leu Phe  
                   225                  230                  235                  240

Gly Val Leu Trp Leu Ala Trp Ser Ala Cys Tyr Trp Arg Asp Leu Leu  
                   245                  250                  255

Arg Ile Gln Phe Trp Ile Gly Ala Val Ile Phe Leu Gly Met Leu Glu  
                   260                  265                  270

Lys Ala Val Phe Tyr Ala Glu Phe Gln Asn Ile Arg Tyr Lys Gly Xaa  
                   275                  280                  285

Ser Val Gln Gly Ala Leu Ile Leu Ala Glu Leu Leu Ser Ala Val Lys  
                   290                  295                  300

Arg Ser Leu Ala Arg Thr Leu Val Ile Ile Val Ser Leu Gly Tyr Gly  
                   305                  310                  315                  320

Ile Val Lys Pro Arg Leu Glu Ser Leu Phe Ile Arg Leu Xaa  
325 330

<213> Homo sapiens

<223> Xaa equals any of the naturally occurring L-amino acids

<223> Xaa equals any of the naturally occurring L-amino acids

<223> Xaa equals stop translation

Met Val Leu Xaa Val Val Thr Leu Gly Leu Ala Leu Phe Thr Leu Cys  
1 5 10 15

Gly Lys Phe Lys Arg Trp Lys Leu Asn Gly Ala Phe Leu Leu Ile Thr  
20 25 30

Ala Phe Leu Ser Val Leu Ile Trp Val Ala Trp Met Thr Met Tyr Leu  
35 40 45

Phe Gly Asn Val Lys Leu Gln Gln Gly Asp Ala Trp Asn Asp Pro Thr  
50 55 60

Leu Ala Ile Thr Leu Ala Ala Ser Ala Gly Ser Ser Ser Ser Ser Thr  
65 70 75 80

Pro Ser Leu Arg Ser Thr Ala Pro Phe Cys Gln Pro Cys Arg Arg Thr  
85 90 95

Arg Pro Thr Thr Ser Thr Arg Arg Ser Pro Gly Cys Gly Arg Arg Pro  
100 105 110

Ser Arg Arg Thr Cys Ser Cys Arg Gly Pro Ile Trp Arg Thr Arg Pro  
115 120 125

Ser Pro Trp Met Asn Thr Met Gln Leu Ser Glu Gln Gln Asp Phe Pro  
130 135 140

Thr Ala Ala Trp Glu Lys Asp Pro Val Ala Ala Trp Gly Lys Asp Pro  
145 150 155 160

Ala Leu Arg Leu Glu Ala Thr Cys Ile Ser Gln Leu Arg Trp Pro Ser  
165 170 175

225

Cys Ser Thr Val Gly Pro Ser Gln Leu Leu Arg Gln Val Thr Gln Glu  
                   180                  185                  190

Xaa Thr Phe Gly Glu Arg Leu Xaa  
           195                  200

<210> 350  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (24)  
 <223> Xaa equals stop translation

<400> 350  
 Met Leu Leu His His Gln Leu Leu Ile Val Thr Leu His Leu Val Leu  
       1                  5                  10                  15

Leu Leu Ala Thr Leu Leu Val Xaa  
                   20

<210> 351  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (85)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (131)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (143)  
 <223> Xaa equals stop translation

<400> 351  
 Met Thr Lys Ala Leu Leu Ile Tyr Leu Val Ser Ser Phe Leu Ala Leu  
       1                  5                  10                  15

Asn Gln Ala Ser Leu Ile Ser Arg Cys Asp Leu Ala Gln Val Leu Gln  
           20                  25                  30

Leu Glu Asp Leu Asp Gly Phe Glu Gly Tyr Ser Leu Ser Asp Trp Leu  
           35                  40                  45

Cys Leu Ala Phe Val Glu Ser Lys Phe Asn Ile Ser Lys Ile Asn Glu  
       50                  55                  60

226

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Asn | Ala | Asp | Gly | Ser | Phe | Asp | Tyr | Gly | Leu | Phe | Gln | Ile | Asn | Ser | His |  |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| Tyr | Trp | Cys | Asn | Xaa | Tyr | Lys | Ser | Tyr | Ser | Glu | Asn | Leu | Cys | His | Val |  |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Asp | Cys | Gln | Asp | Leu | Leu | Asn | Pro | Asn | Leu | Leu | Ala | Gly | Ile | His | Cys |  |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| Ala | Lys | Arg | Ile | Val | Ser | Gly | Ala | Arg | Gly | Met | Asn | Asn | Trp | Val | Arg |  |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| Met | Glu | Xaa | Cys | Thr | Val | Gln | Ala | Gly | His | Ser | Ser | Thr | Gly | Xaa |     |  |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |

```
<210> 352
<211> 95
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (95)
<223> Xaa equals stop translation
```

```

<400> 352
Met Leu Val Ile Ala Gly Gly Ile Leu Ala Ala Leu Leu Leu Leu Ile
  1             5             10             15
Val Val Val Leu Cys Leu Tyr Phe Lys Ile His Asn Ala Leu Lys Ala
      20             25             30
Ala Lys Glu Pro Glu Ala Val Ala Val Lys Asn His Asn Pro Asp Lys
      35             40             45
Val Trp Trp Ala Lys Asn Ser Gln Ala Lys Thr Ile Ala Thr Glu Ser
  .50             55             60
Cys Pro Ala Leu Gln Cys Cys Glu Gly Tyr Arg Met Cys Ala Ser Phe
  65             70             75             80
Asp Ser Leu Pro Pro Cys Cys Cys Asp Ile Asn Glu Gly Leu Xaa
      85             90             95

```

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<210> 353
<211> 38
<212> PRT
<213> Homo sapiens
```

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<220>
<221> SITE
<222> (38)
<223> Xaa equals stop translation
```

<400> 353  
Met Leu Leu Lys Ser Asn Ile Leu Met Leu Asn Leu Phe Ala Ala Asn



227

1                    5                    10                    15  
 Val Gly Ala Asn Phe Ala Leu Thr Val Glu Lys Ile Gly Met Ile Leu  
                   20                    25                    30

Leu Asn Val Ser Gly Xaa  
                   35

<210> 354  
 <211> 39  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (39)  
 <223> Xaa equals stop translation

<400> 354  
 Met Leu Val Val Ala Phe Gly Leu Leu Val Leu Tyr Ile Leu Leu Ala  
   1                    5                    10                    15

Ser Ser Trp Lys Arg Pro Glu Pro Gly Ile Leu Thr Asp Arg Gln Pro  
                   20                    25                    30

Leu Leu His Asp Gly Glu Xaa  
                   35

<210> 355  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (35)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (71)  
 <223> Xaa equals stop translation

<400> 355  
 Ser Asp Pro Leu Ala Ser Ala Ser Gln Asn Ala Gly Ile Val Ser Val  
   1                    5                    10                    15

Gly Leu Cys Thr Arg Pro Gly Pro Gln Phe Lys Asn Ala Gln Pro Pro  
                   20                    25                    30

Phe Pro Xaa Gln Lys Ala Pro Arg Cys Leu Trp Glu Asn Gln Pro Pro  
                   35                    40                    45

Pro Trp Arg Lys Ala Trp Asp Leu Pro Ser His Leu Gly Arg Arg Gly  
                   50                    55                    60

228

Ile Cys Gly Lys Ser Phe Xaa  
65 70

&lt;210&gt; 356

&lt;211&gt; 227

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 356

Met Ala Asp Leu Leu Gly Ser Ile Leu Ser Ser Met Glu Lys Pro Pro  
1 5 10 15

Ser Leu Gly Asp Gln Glu Thr Arg Arg Lys Ala Arg Glu Gln Ala Ala  
20 25 30

Arg Leu Lys Lys Leu Gln Glu Gln Glu Lys Gln Gln Lys Val Glu Phe  
35 40 45

Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp Ser Gly  
50 55 60

Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg Ser Ile  
65 70 75 80

Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser Phe Gly  
85 90 95

Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu Phe Ala  
100 105 110

Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu Trp Asp  
115 120 125

Pro Gln Lys Ala Glu Glu Lys Arg Lys Leu Lys Glu Leu Ala Gln Arg  
130 135 140

Gln Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser Pro Ala  
145 150 155 160

Ser Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly Ala Ala  
165 170 175

Lys Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly Cys Val  
180 185 190

Pro Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala Met Asn  
195 200 205

Glu Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu Glu Leu Pro  
210 215 220

Pro Thr Ser  
225

&lt;210&gt; 357

&lt;211&gt; 90

229

<212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (50)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (53)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (60)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (64)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (65)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (90)  
 <223> Xaa equals stop translation

<400> 357

Met Trp Asp Trp Asp Trp Ser Ala Pro Trp Ser Trp Pro Leu Trp Leu  
 1 5 10 15

Ser Leu Ala Leu Val Cys Leu Ser Ala Gly Ala Lys Gly His Arg Ala  
 20 25 30

Ser Glu Ala Gly His Ala Arg Ala Leu Thr Cys Glu Met Gly Ser Glu  
 35 40 45

Phe Xaa Thr Ala Xaa Gly Leu Val Leu Gly Xaa Xaa Xaa Trp Thr Xaa  
 50 55 60

Xaa Asn Gly Ser Ala Gly Pro Glu Arg Arg Gly Trp Arg Pro Ala Ala  
 65 70 75 80

230

Phe Leu Ala Val Phe Leu Leu Gly Asp Xaa  
                   85                  90

&lt;210&gt; 358

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 358

Met Phe Gly Pro Thr Phe His Ser Leu Val Leu Val Pro Pro Trp Pro  
   1                  5                  10                  15

Asn Leu Ser Leu Leu His Phe Thr Ser Pro Val Gly Gln His Ser Ser  
                   20                  25                  30

Phe Leu Pro Thr Ser Leu Arg Leu Xaa Lys Lys Lys Lys Lys Lys Lys  
           35                  40                  45

&lt;210&gt; 359

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 359

Met Cys Ser Lys Asn Gly Phe Leu Leu Ala Trp Ser Trp Asn Ser Pro  
   1                  5                  10                  15

Trp Leu Pro Gln Ala Ser Leu Ala His Gly Cys Trp Gly Arg Trp Met  
           20                  25                  30

Ser Asp Leu Val Gly Cys Ser Arg Glu Asn Lys Cys Ala Leu Arg Asp  
           35                  40                  45

His Ser Glu Arg Val Gln Gly Xaa  
       50                  55

&lt;210&gt; 360

&lt;211&gt; 222

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

231

<220>  
 <221> SITE  
 <222> (4)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (222)  
 <223> Xaa equals stop translation

<400> 360  
 Ser Pro Leu Xaa Phe Cys Val Val Leu Leu Leu Gln Ala Ala Arg Gly  
 1 5 10 15  
 Tyr Val Val Arg Lys Pro Ala Gln Ser Arg Leu Asp Asp Asp Pro Pro  
 20 25 30  
 Pro Ser Thr Leu Leu Lys Asp Tyr Gln Asn Val Pro Gly Ile Glu Lys  
 35 40 45  
 Val Asp Asp Val Val Lys Arg Leu Leu Ser Leu Glu Met Ala Asn Lys  
 50 55 60  
 Lys Glu Met Leu Lys Ile Lys Gln Glu Gln Phe Met Lys Lys Ile Val  
 65 70 75 80  
 Ala Asn Pro Glu Asp Thr Arg Ser Leu Glu Ala Arg Ile Ile Ala Leu  
 85 90 95  
 Ser Val Lys Ile Arg Ser Tyr Glu Glu His Leu Glu Lys His Arg Lys  
 100 105 110  
 Asp Lys Ala His Lys Arg Tyr Leu Leu Met Ser Ile Asp Gln Arg Lys  
 115 120 125  
 Lys Met Leu Lys Asn Leu Arg Asn Thr Asn Tyr Asp Val Phe Glu Lys  
 130 135 140  
 Ile Cys Trp Gly Leu Gly Ile Glu Tyr Thr Phe Pro Pro Leu Tyr Tyr  
 145 150 155 160  
 Arg Arg Ala His Arg Arg Phe Val Thr Lys Lys Ala Leu Cys Ile Arg  
 165 170 175  
 Val Phe Gln Glu Thr Gln Lys Leu Lys Lys Arg Arg Arg Ala Leu Lys  
 180 185 190  
 Ala Ala Ala Ala Ala Gln Lys Gln Ala Lys Arg Arg Asn Pro Asp Ser  
 195 200 205  
 Pro Ala Lys Ala Ile Pro Lys Thr Leu Lys Asp Ser Gln Xaa  
 210 215 220

<210> 361  
 <211> 432

232

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 361

Met Gly Ala Pro Ala Ala Ser Leu Leu Leu Leu Leu Leu Phe Ala  
 1 5 10 15

Cys Cys Trp Ala Pro Gly Gly Ala Asn Leu Ser Gln Asp Gly Tyr Trp  
 20 25 30

Gln Glu Gln Asp Leu Glu Leu Gly Thr Leu Ala Pro Leu Asp Glu Ala  
 35 40 45

Ile Ser Ser Thr Val Trp Ser Ser Pro Asp Met Leu Ala Ser Gln Asp  
 50 55 60

Ser Gln Pro Trp Thr Ser Asp Glu Thr Val Val Ala Gly Gly Thr Val  
 65 70 75 80

Val Leu Lys Cys Gln Val Lys Asp His Glu Asp Ser Ser Leu Gln Trp  
 85 90 95

Ser Asn Pro Ala Gln Gln Thr Leu Tyr Phe Gly Glu Lys Arg Ala Leu  
 100 105 110

Arg Asp Asn Arg Ile Gln Leu Val Thr Ser Thr Pro His Glu Leu Ser  
 115 120 125

Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu Tyr Thr Cys  
 130 135 140

Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu Val Thr Val  
 145 150 155 160

Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys Ser Ser Leu  
 165 170 175

Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser Gly Ser Lys  
 180 185 190

Pro Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu Leu His Gly  
 195 200 205

Glu Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr Phe Thr Val  
 210 215 220

Ser Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp Gly Ala Ser  
 225 230 235 240

Ile Val Cys Ser Val Asn His Glu Ser Leu Lys Gly Ala Asp Arg Ser  
 245 250 255

Thr Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala Met Ile Arg  
 260 265 270

Pro Asp Pro Pro His Pro Arg Glu Gly Gln Lys Leu Leu Leu His Cys  
 275 280 285

233

Glu Gly Arg Gly Asn Pro Val Pro Gln Gln Tyr Leu Trp Glu Lys Glu  
 290 295 300  
 Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser Ala Leu Ile Phe  
 305 310 315 320  
 Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys Thr Ala Thr  
 325 330 335  
 Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu Asn Val Asn Asp  
 340 345 350  
 Pro Ser Pro Val Pro Ser Ser Ser Ser Thr Tyr His Ala Ile Ile Gly  
 355 360 365  
 Gly Ile Val Ala Phe Ile Val Phe Leu Leu Leu Ile Met Leu Ile Phe  
 370 375 380  
 Leu Gly His Tyr Leu Ile Arg His Lys Gly Thr Tyr Leu Thr His Glu  
 385 390 395 400  
 Ala Lys Gly Ser Asp Asp Ala Pro Asp Ala Asp Thr Ala Ile Ile Asn  
 405 410 415  
 Ala Glu Gly Gly Gln Ser Gly Gly Asp Asp Lys Lys Glu Tyr Phe Ile  
 420 425 430

&lt;210&gt; 362

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (111)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (125)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (135)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (144)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

234

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (154)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 362

Met Val Ala Pro Val Trp Tyr Leu Val Ala Ala Ala Leu Leu Val Gly  
 1 5 10 15

Phe Ile Leu Phe Leu Thr Arg Ser Arg Gly Arg Ala Ala Ser Ala Gly  
 20 25 30

Gln Glu Pro Leu His Asn Glu Glu Leu Ala Gly Ala Gly Arg Val Ala  
 35 40 45

Gln Pro Gly Pro Leu Glu Pro Glu Glu Pro Arg Ala Gly Gly Arg Pro  
 50 55 60

Arg Arg Arg Arg Asp Leu Gly Ser Arg Leu Gln Ala Gln Arg Arg Ala  
 65 70 75 80

Gln Arg Val Ala Trp Ala Glu Ala Asp Glu Asn Glu Glu Glu Ala Val  
 85 90 95

Ile Leu Ala Gln Glu Glu Glu Gly Val Glu Lys Pro Ala Glu Xaa His  
 100 105 110

Leu Ser Gly Lys Ile Gly Ala Lys Lys Leu Arg Xaa Xaa Glu Glu Lys  
 115 120 125

Gln Ala Arg Lys Ala Gln Xaa Glu Ala Glu Glu Ala Glu Arg Glu Xaa  
 130 135 140

Arg Lys Arg Leu Glu Ser Gln Arg Glu Xaa  
 145 150

&lt;210&gt; 363

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 363

Met Gln Lys Cys Met Leu Ser Ala Leu Val Phe His Ile Gln Trp Ser  
 1 5 10 15

Xaa

&lt;210&gt; 364

&lt;211&gt; 10



235

<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (10)  
<223> Xaa equals stop translation

<400> 364  
Met Leu Val Cys Ser Phe Leu Phe Leu Xaa  
1 5 10

<210> 365  
<211> 14  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (14)  
<223> Xaa equals stop translation

<400> 365  
Val Ile Glu Leu Cys Val Ser Leu Arg Ser Leu Asn Phe Xaa  
1 5 10

<210> 366  
<211> 18  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (5)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (6)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (7)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (10)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (18)  
<223> Xaa equals stop translation

236

&lt;400&gt; 366

Met Cys Glu Phe Xaa Xaa Xaa Ile Met Xaa Leu Ala Gly Tyr Phe Ala  
1 5 10 15

Cys Xaa

&lt;210&gt; 367

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (62)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 367

Met Val Gly Gly Tyr Val Ser Ser Phe Ser Phe Pro Pro Val Ser Ser  
1 5 10 15

Ser Leu Leu Leu Pro Ala Ser Phe Ala Phe Pro Phe Leu Pro Gly Thr  
20 25 30

Pro Cys Pro Phe Leu Tyr Phe Leu Pro Ser Pro Phe Ser Pro Leu Pro  
35 40 45

Leu Ser Leu Thr Arg Ser Asn Ser Phe Leu Leu Asn Gly Xaa  
50 55 60

&lt;210&gt; 368

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 368

Glu Lys Lys Ser Met Ser Val Ser Asp Ile Tyr Ala Leu Glu Ser Leu  
1 5 10 15

Gly Arg Ser Leu Phe Thr Leu Asn Ser Met Cys Leu Pro Leu Ser Phe  
20 25 30

Xaa

&lt;210&gt; 369

&lt;211&gt; 245

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

237

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (79)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 369

Met Gly Gly Ala Ser Arg Arg Val Glu Ser Gly Ala Trp Ala Tyr Leu  
 1 5 10 15

Ser Pro Leu Val Leu Arg Lys Glu Leu Glu Ser Leu Val Glu Asn Glu  
 20 25 30

Gly Ser Glu Val Leu Ala Leu Pro Glu Leu Pro Ser Ala His Pro Ile  
 35 40 45

Ile Phe Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser  
 50 55 60

Ile Leu Pro Gly Leu Val Leu Ala Ser Cys Asp Gly Pro Ser Xaa Ser  
 65 70 75 80

Gln Ala Pro Ser Pro Trp Leu Thr Pro Asp Pro Ala Ser Val Gln Val  
 85 90 95

Arg Leu Leu Trp Asp Val Leu Thr Pro Asp Pro Asn Ser Cys Pro Pro  
 100 105 110

Leu Tyr Val Leu Trp Arg Val His Ser Gln Ile Pro Gln Arg Val Val  
 115 120 125

Trp Pro Gly Pro Val Pro Ala Ser Leu Ser Leu Ala Leu Leu Glu Ser  
 130 135 140

Val Leu Arg His Val Gly Leu Asn Glu Val His Lys Ala Val Gly Leu  
 145 150 155 160

Leu Leu Glu Thr Leu Gly Pro Pro Pro Thr Gly Leu His Leu Gln Arg  
 165 170 175

Gly Ile Tyr Arg Glu Ile Leu Phe Leu Thr Met Ala Ala Leu Gly Lys  
 180 185 190

Asp His Val Asp Ile Val Ala Phe Asp Lys Lys Tyr Lys Ser Ala Phe  
 195 200 205

Asn Lys Leu Ala Ser Ser Met Gly Lys Glu Glu Leu Arg His Arg Arg  
 210 215 220

Ala Gln Met Pro Thr Pro Lys Ala Ile Asp Cys Arg Lys Cys Phe Gly  
 225 230 235 240

Ala Pro Pro Glu Cys  
 245

&lt;210&gt; 370

&lt;211&gt; 35

&lt;212&gt; PRT

238

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 370

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Phe | Ser | Leu | Leu | Phe | Leu | Pro | Met | Leu | Leu | Ile | Leu | Lys | Pro |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Leu | Phe | His | Ile | Ser | Ile | Cys | Thr | Leu | Ala | Ala | Cys | Gly | Leu | Thr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |
|-----|-----|-----|
| Phe | Pro | Xaa |
|     |     | 35  |

&lt;210&gt; 371

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 371

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Leu | Phe | Phe | Phe | Ile | Leu | His | Leu | Leu | Ser | Ile | Met | Ser | Phe | Leu |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |

|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
| Ser | Pro | Asp | Ile | Met | Xaa |
|     |     |     | 20  |     |     |

&lt;210&gt; 372

&lt;211&gt; 98

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 372

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Phe | Gly | Leu | Leu | Val | Glu | Ser | Gln | Thr | Leu | Leu | Glu | Glu | Asn | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Gly | Thr | Glu | Arg | Thr | Leu | Gly | Leu | Asn | Ile | Ala | Pro | Phe | Ile |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Gln | Phe | Gln | Val | Pro | Ile | Arg | Val | Phe | Leu | Asp | Leu | Ser | Ser | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Cys | Ile | Pro | Leu | Ser | Lys | Pro | Val | Glu | Leu | Leu | Arg | Leu | Asp | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     |     | 60  |     |     |     |

239

Met Thr Pro Tyr Leu Asn Thr Ser Asn Arg Glu Val Lys Val Tyr Val  
 65 70 75 80

Cys Xaa Ile Trp Glu Asp Leu Thr Ala Ile Pro Phe Trp Val Ser Tyr  
 85 90 95

Val Pro

<210> 373

<211> 78

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 373

Met Phe Gly Ala His Arg Xaa Trp Gln Gly Ser Val Leu Leu Phe Leu  
 1 5 10 15

Ser Phe Ala Trp Gly Asn Gly Gly Ser Val Thr Phe Ser Asp Val Pro  
 20 25 30

Arg Val Met Pro Leu Ala Gly Gly Pro Xaa Xaa Gln Val Ser Ser Thr  
 35 40 45

Pro Arg Pro Pro Pro His Gln Val Thr Ser Ser Pro Gly Leu Glu Ser  
 50 55 60

Ala His Ile Val Cys Pro Glu Arg Lys Lys Lys Lys Lys Lys  
 65 70 75

<210> 374

<211> 31

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

240

<220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (20)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (28)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals stop translation

<400> 374  
 Thr Leu Leu Xaa Phe Leu Xaa Leu Leu Thr Thr Glu Gly Gly Arg Glu  
 1 5 10 15  
 Asn Ile Phe Xaa Gly Arg Ile Leu Xaa Leu Gln Xaa Ser Pro Xaa  
 20 25 30

<210> 375  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals stop translation

<400> 375  
 Met Leu Ser Phe Phe Ile Cys Leu Leu Ile Phe Val His Leu Leu Leu  
 1 5 10 15  
 Leu Ser Phe Leu Ile Ser Asp Trp Pro Pro Pro Thr Gly Ser Ala Xaa  
 20 25 30  
 His Lys Ile Leu Arg Leu Met Val Val Gln Arg Leu Ser Leu Leu Asp  
 35 40 45

241

Gln Arg Lys Arg Trp Ser Glu Ala Xaa  
 50 55

<210> 376  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (14)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 376  
 Met Cys His His Ala Trp Leu Ile Phe Lys Phe Phe Val Xaa Met Gly  
 1 5 10 15  
 Ser His Tyr Val Ala Gln Ala Gly Phe Arg Phe Leu Cys Ser Arg Asp  
 20 25 30  
 Ser Ala Asn Leu Ala Pro Gln Ser Ala Gly Ile Thr Asn Val Ser His  
 35 40 45  
 Cys Ile Trp Pro Ile Phe Phe Phe Lys Lys Lys Met Gln Arg Cys  
 50 55 60

<210> 377  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 377  
 Met Thr Met Val Leu Cys Ile Phe Ile Leu Gly His His Ala Arg Glu  
 1 5 10 15  
 Asp Pro Pro Ser Asn Gly His Ile Thr Ser Glu Gly Ala Phe Leu Val  
 20 25 30  
 Asn Val Gly Ala Pro Gln  
 35

<210> 378  
 <211> 98  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 378  
 Met Leu Arg Leu Glu Ala Arg Ala Thr Thr Pro Gly Leu Gln Thr His  
 1 5 10 15

242

Ser Cys Leu Gly Phe Tyr Ile Lys Tyr Glu His Lys Asn Thr Phe Pro  
           20                          25                          30  
 Lys Tyr Ser Leu Trp Leu Cys Leu Thr Leu Gly Thr Xaa Pro Ser Thr  
           35                          40                          45  
 Ser Ser Ile Leu Arg Tyr Val Arg Gly Val Tyr Arg Gly Leu Glu Tyr  
           50                          55                          60  
 Ile Arg Phe Phe Ser Asn Ser Ser Ser Ser Arg Arg Arg Leu Thr Thr  
           65                          70                          75                          80  
 Ser Leu Gly Phe Lys Val Ser Gly Leu Lys Phe Pro Pro Glu Ile Thr  
                           85                          90                          95  
 Ile Arg

<210> 379  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals stop translation

<400> 379  
 Thr Leu Thr Ser Phe Leu Glu Leu Pro Leu Ala Pro Glu Pro Xaa  
       1                          5                          10                          15

<210> 380  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals stop translation

<400> 380  
 Met His Arg Tyr Ile Thr Phe Phe Lys Cys Phe Arg Ser Val Ile Leu  
       1                          5                          10                          15

Asp Leu Leu Phe Ile Leu Ser Pro Leu Ser Gln Gly Cys Phe Ile Leu  
           20                          25                          30

Phe Xaa

<210> 381  
 <211> 66  
 <212> PRT



243

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (62)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 381

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Phe | Gly | Phe | Ile | Phe | Leu | Leu | Leu | Ile | Phe | Cys | Ile | Xaa | Leu | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Thr | Leu | Ser | Thr | Phe | Ile | Pro | Lys | Leu | Val | Gly | Phe | Leu | Tyr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Lys | Phe | Ser | Ile | Asn | Leu | Ser | Leu | Leu | Leu | Thr | Leu | Ile | Lys | Lys |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Lys | Lys | Lys | Lys | Lys | Thr | Pro | Arg | Gly | Gly | Pro | Gly | Xaa | Gln | Ser |
|     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

Pro Pro

65

&lt;210&gt; 382

&lt;211&gt; 317

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (207)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 382

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Pro | Gly | Leu | Gly | Arg | Pro | Arg | Gln | Ala | Arg | Trp | Thr | Leu | Met | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Ser | Thr | Ala | Met | Tyr | Gly | Ala | His | Ala | Pro | Leu | Leu | Ala | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | His | Val | Asp | Gly | Arg | Val | Pro | Phe | Arg | Pro | Ser | Ser | Ala | Val | Leu |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Thr | Glu | Leu | Thr | Lys | Leu | Leu | Leu | Cys | Ala | Phe | Ser | Leu | Leu | Val |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Trp | Gln | Ala | Trp | Pro | Gln | Gly | Pro | Pro | Pro | Trp | Arg | Gln | Ala | Ala |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Phe | Ala | Leu | Ser | Ala | Leu | Leu | Tyr | Gly | Ala | Asn | Asn | Asn | Leu | Val |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

244

Ile Tyr Leu Gln Arg Tyr Met Asp Pro Ser Thr Tyr Gln Val Leu Ser  
                   100                  105                  110  
 Asn Leu Lys Ile Gly Ser Thr Ala Val Leu Tyr Cys Leu Cys Leu Arg  
                   115                  120                  125  
 His Arg Leu Ser Val Arg Gln Gly Leu Ala Leu Leu Leu Met Ala  
                   130                  135                  140  
 Ala Gly Ala Cys Tyr Ala Ala Gly Gly Leu Gln Val Pro Gly Asn Thr  
                   145                  150                  155                  160  
 Leu Pro Ser Pro Pro Pro Ala Ala Ala Ala Ser Pro Met Pro Leu His  
                   165                  170                  175  
 Ile Thr Pro Leu Gly Leu Leu Leu Leu Ile Leu Tyr Cys Leu Ile Ser  
                   180                  185                  190  
 Gly Leu Ser Ser Val Tyr Thr Glu Leu Leu Met Lys Arg Gln Xaa Leu  
                   195                  200                  205  
 Pro Leu Ala Leu Gln Asn Leu Phe Leu Tyr Thr Phe Gly Val Leu Leu  
                   210                  215                  220  
 Asn Leu Gly Leu His Ala Gly Gly Gly Ser Gly Pro Gly Leu Leu Glu  
                   225                  230                  235                  240  
 Gly Phe Ser Gly Trp Ala Ala Leu Val Val Leu Ser Gln Ala Leu Asn  
                   245                  250                  255  
 Gly Leu Leu Met Ser Ala Val Met Lys His Gly Ser Ser Ile Thr Arg  
                   260                  265                  270  
 Leu Phe Val Val Ser Cys Ser Leu Val Val Asn Ala Val Leu Ser Ala  
                   275                  280                  285  
 Val Leu Leu Arg Leu Gln Leu Thr Ala Ala Phe Phe Leu Ala Thr Leu  
                   290                  295                  300  
 Leu Ile Gly Leu Ala Met Arg Leu Tyr Tyr Gly Ser Arg  
                   305                  310                  315

&lt;210&gt; 383

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (23)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

245

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 383

Met Gly Glu Gln Pro His Phe Ser Leu Cys Val Leu Leu Ala Ala Val  
1 5 10 15

Arg Glu Asp Xaa Asp Pro Xaa Val Phe Pro Cys Cys Phe Leu Xaa  
20 25 30

&lt;210&gt; 384

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 384

Met Ser Phe Ile Ala Leu His Pro Leu Leu Pro Glu Ala Ala Leu Gly  
1 5 10 15

Val Pro Gly Gln Ser Pro His Arg Pro Leu Trp Gln Thr Gln Cys Cys  
20 25 30

Val Ala Pro Pro Gln Pro Arg Ala Glu Phe Xaa  
35 40

&lt;210&gt; 385

&lt;211&gt; 255

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (255)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 385

Met Val Thr Ala Leu Thr Leu Leu Ala Phe Pro Leu Leu Leu Leu His  
1 5 10 15

Ala Glu Arg Ile Ser Leu Val Phe Leu Leu Leu Phe Leu Gln Ser Phe  
20 25 30

Leu Leu Leu His Leu Leu Ala Ala Gly Ile Pro Val Thr Thr Pro Gly  
35 40 45

Pro Phe Thr Val Pro Trp Gln Ala Val Ser Ala Trp Ala Leu Met Ala  
50 55 60

Thr Gln Thr Phe Tyr Ser Thr Gly His Gln Pro Val Phe Pro Ala Ile

246

|             |   |                             |     |    |  |     |
|-------------|---|-----------------------------|-----|----|--|-----|
| 65          |   | 70                          |     | 75 |  | 80  |
| His Trp His | Ala Ala Phe Val Gly Phe                             | Pro Glu Gly His Gly Ser Cys |     |    |  |     |
|             | 85  | 90                          | 95  |    |  |     |
| Thr Trp Leu | Pro Ala Leu Leu Val Gly Ala Asn Thr Phe Ala Ser His |                             |     |    |  |     |
|             | 100   | 105                         | 110 |    |  |     |
| Leu Leu Phe | Ala Val Gly Cys Pro Leu Leu Leu Leu Trp Pro Phe Leu |                             |     |    |  |     |
|             | 115   | 120                         | 125 |    |  |     |
| Cys Glu Ser | Gln Gly Leu Arg Lys Arg Gln Gln Pro Pro Gly Asn Glu |                             |     |    |  |     |
|             | 130   | 135                         | 140 |    |  |     |
| Ala Asp Ala | Arg Val Arg Pro Glu Glu Glu Glu Glu Pro Leu Met Glu |                             |     |    |  |     |
|             | 145   | 150                         | 155 |    |  | 160 |
| Met Arg Leu | Arg Asp Ala Pro Gln His Phe Tyr Ala Ala Leu Leu Gln |                             |     |    |  |     |
|             | 165   | 170                         | 175 |    |  |     |
| Leu Gly Leu | Lys Tyr Leu Phe Ile Leu Gly Ile Gln Ile Leu Ala Cys |                             |     |    |  |     |
|             | 180   | 185                         | 190 |    |  |     |
| Ala Leu Ala | Ala Ser Ile Leu Arg Arg His Leu Met Val Trp Lys Val |                             |     |    |  |     |
|             | 195   | 200                         | 205 |    |  |     |
| Phe Ala Pro | Lys Phe Ile Phe Glu Ala Val Gly Phe Ile Val Ser Ser |                             |     |    |  |     |
|             | 210   | 215                         | 220 |    |  |     |
| Val Gly Leu | Leu Leu Gly Ile Ala Leu Val Met Arg Val Asp Gly Ala |                             |     |    |  |     |
|             | 225   | 230                         | 235 |    |  | 240 |
| Val Ser Ser | Trp Phe Arg Gln Leu Phe Leu Ala Gln Gln Arg Xaa     |                             |     |    |  |     |
|             | 245   | 250                         | 255 |    |  |     |

&lt;210&gt; 386

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 386

|             |   |
|-------------|---|
| Met Xaa Gly | Pro Trp Gly Glu Glu Ala Leu Ile Arg Leu Pro Thr Pro |
| 1           | 5 10 15   |

|                 |
|-----------------|
| Ser Gly Leu Xaa |
| 20              |

247

&lt;210&gt; 387

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 387

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ala | Thr | Leu | Glu | Xaa | Asn | Gln | Arg | Glu | Val | Asp | Arg | Glu | Ile | Arg |
| 1   |     |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Leu | Leu | Trp | Phe | Leu | Leu | Cys | Glu | Ile | Val | Ser | Gly | Trp | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Pro | Glu | Gly | Pro | Trp | Phe | Ser | Gln | Gly | Cys | Gln | Ile | Tyr | Lys | Asn |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ser | Ser | Ser | Ser | Ser | Tyr | Asn | Leu | Ser | Phe | Leu | Leu | Ser | Leu | Xaa |
|     |     |     | 50  |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

&lt;210&gt; 388

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (40)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 388

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | His | Ser | Gly | Cys | Thr | Ser | Gln | Cys | Leu | Glu | Gly | Phe | Phe | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Phe | Leu | Leu | Asp | Phe | Asn | Pro | Val | Leu | Ala | Leu | Asp | Leu | Ile | Gly |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Met | Arg | Lys | Ala | Ser | His | Xaa |
|     |     |     | 35  |     |     | 40  |     |

&lt;210&gt; 389

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

248

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<220>
<221> SITE
<222> (35)
<223> Xaa equals stop translation

<400> 389
Met Val Phe Ser Ala Arg Val Ser Leu Tyr Thr Arg Phe Lys Val Ile
 1             5             10             15

Leu Leu Ser Leu Leu Ile Met Ile Leu His Val Cys Trp Val Trp Val
      20             25             30

Ile Leu Xaa
      35

<210> 390
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (11)
<223> Xaa equals stop translation

<400> 390
Gly Leu Leu Tyr Ile Met Tyr Cys Asn Ile Xaa
 1             5             10

<210> 391
<211> 64
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (64)
<223> Xaa equals stop translation

<400> 391
Met Asn Asn Gly Leu Leu Gln Gln Pro Ser Ala Leu Met Leu Leu Pro
 1             5             10             15

Cys Arg Pro Val Leu Thr Ser Val Ala Leu Asn Ala Asn Phe Val Ser
      20             25             30

Trp Lys Ser Arg Thr Lys Tyr Thr Ile Thr Pro Val Lys Met Arg Lys
      35             40             45

Ser Gly Gly Arg Asp His Thr Gly Gly Asn Lys Asp Arg Gly Ile Xaa
      50             55             60

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249

<210> 392  
<211> 19  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals stop translation

<400> 392  
Met Arg Lys Gln Arg Leu Val Pro Met Tyr Leu Gly Leu Ile Tyr Ile  
1 5 10 15  
Leu Leu Xaa

<210> 393  
<211> 43  
<212> PRT  
<213> Homo sapiens

<400> 393  
Met Glu Ile Ser Val Ile Lys Ile Phe Gln Asp Glu Thr Thr Leu Lys  
1 5 10 15  
Ile Lys Leu Cys Leu Val Ser Leu Ser Ser Leu Leu Val Ser Leu Leu  
20 25 30  
Leu Leu Ile Leu Pro Glu Ser Thr Ser Leu Trp  
35 40

<210> 394  
<211> 17  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (17)  
<223> Xaa equals stop translation

<400> 394  
Leu Leu Leu Pro Val Leu Ala Ser Ser Val Pro Ser His Ser Ala Thr  
1 5 10 15  
Xaa

<210> 395  
<211> 84  
<212> PRT  
<213> Homo sapiens

250

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (84)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 395

Met Leu Pro Leu Leu Leu Phe Thr Tyr Leu Asn Ser Phe Leu His Gln  
 1 5 10 15

Arg Ile Pro Gln Ser Val Arg Ile Leu Gly Ser Leu Val Ala Ile Leu  
 20 25 30

Leu Val Phe Leu Ile Thr Ala Ile Leu Val Lys Val Gln Leu Asp Ala  
 35 40 45

Leu Pro Phe Phe Val Ile Thr Met Ile Lys Ile Val Leu Ile Asn Ser  
 50 55 60

Phe Gly Ala Ile Leu Gln Gly Ser Leu Phe Gly Leu Ala Gly Leu Leu  
 65 70 75 80

Pro Ala Ser Xaa

&lt;210&gt; 396

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 396

Met Lys Leu Ser Leu Phe Leu Ile Leu Ser Asp Val Phe Tyr Leu Gly  
 1 5 10 15

Ser Pro Xaa Thr Xaa  
 20

&lt;210&gt; 397

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals stop translation



251

&lt;400&gt; 397

Met Gly Thr Arg Arg Lys Gly Val Ala Trp Leu Ser Leu Ala Pro Leu  
1 5 10 15

Ile Thr Gly Leu Ala Pro Ala His Ile Thr Ala Val Xaa  
20 25

&lt;210&gt; 398

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 398

Met Lys Asp Leu Leu Gln Arg Asn Pro Trp Lys Asn Ser Leu Leu Leu  
1 5 10 15

Leu Gln Val Cys Gln Ala Phe Leu Val Cys Ser Leu Thr Gln Leu Ala  
20 25 30

Val Xaa

&lt;210&gt; 399

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 399

Met Ser Glu Ser His Lys Ile Trp Trp Cys Tyr Arg His Leu Ala Phe  
1 5 10 15

Pro Leu Leu Thr Leu Ile Leu Tyr Pro Ala Thr Leu Gly Arg Ser Val  
20 25 30

Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Xaa  
35 40 45

&lt;210&gt; 400

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

252

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 400

Met Leu Asn Arg Ile Met Val Ala Ser Phe Gly Ala Val Leu Val Gln  
 1 5 10 15

Val Cys Arg Gly Xaa Gly Gln Gly Xaa  
 20 25

&lt;210&gt; 401

&lt;211&gt; 68

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 401

Met Gln Leu Leu Leu Gly Leu Ile Arg Ser Gln Pro Ser Pro Pro  
 1 5 10 15

Pro Ser Leu Cys Leu Met Leu Cys Pro Cys Leu Pro Cys Leu Arg Tyr  
 20 25 30

Ser Pro Phe Val Pro Gln His Pro Cys Pro Leu Pro Leu Asp Leu Cys  
 35 40 45

Leu Ala Gly Cys Ser Ser Leu Ser Val Gln Asp Lys Cys Ser Trp Pro  
 50 55 60

Tyr Pro Ile Xaa  
 65

&lt;210&gt; 402

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 402

Met Lys Asp Ser Leu Cys Arg Val Ser Phe Leu Lys Asn Gln Ile Phe  
 1 5 10 15

Leu Ser Tyr Ile Thr Leu Val Leu Ile Gly His Ala His Phe Ser Gly  
 20 25 30

Val Pro His Tyr Asn Val Ser Phe Val Leu Arg Ile Asn Leu Gln Lys  
 35 40 45

His Leu Lys Ile Thr Thr Ser Asn Gly Ile Glu Ser Lys Lys Thr Gly

253

50                      55                      60

Glu Arg Gly Glu Thr Met Phe Phe Arg Thr Arg Gly Ser Thr His Ala  
 65                      70                      75                      80

Ser Ala Asp Ala Trp  
                                  85

&lt;210&gt; 403

&lt;211&gt; 82

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 403

Met Gly Gly Ser Leu Leu Pro Gln Val Ser Ala Ala Val Leu Xaa Leu  
 1                      5                      10                      15

Asp Gly Leu Leu Leu Pro Gly Leu Lys Gly Cys Gly Pro Leu Arg Val  
                                  20                      25                      30

Ser Phe Pro Gln Ala Lys Phe Lys Ala Ala Ala Leu Cys Glu Ala Leu  
                                  35                      40                      45

Leu Ala Leu Gly Trp Arg Glu Asn Phe Lys Leu Phe Cys Ser Gln Gly  
                                  50                      55                      60

Arg Gly Met Gly Pro Gly Cys Arg Cys Pro His Ser Ala Asn Glu Ser  
 65                      70                      75                      80

Phe Val

&lt;210&gt; 404

&lt;211&gt; 286

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 404

Met Ala Met Glu Gly Tyr Trp Arg Phe Leu Ala Leu Leu Gly Ser Ala  
 1                      5                      10                      15

Leu Leu Val Gly Phe Leu Ser Val Ile Phe Ala Leu Val Trp Val Leu  
                                  20                      25                      30

His Tyr Arg Glu Gly Leu Gly Trp Asp Gly Ser Ala Leu Glu Phe Asn  
                                  35                      40                      45

Trp His Pro Val Leu Met Val Thr Gly Phe Val Phe Ile Gln Gly Ile  
                                  50                      55                      60

Ala Ile Ile Val Tyr Arg Leu Pro Trp Thr Trp Lys Cys Ser Lys Leu

254

|   |     |    |     |    |     |     |
|---|-----|----|-----|----|-----|-----|
| 65  |     | 70 |     | 75 |     | 80  |
| Leu Met Lys Ser Ile His Ala Gly Leu Asn Ala Val Ala Ala Ile Leu | 85  |    | 90  |    | 95  |     |
| Ala Ile Ile Ser Val Val Ala Val Phe Glu Asn His Asn Val Asn Asn | 100 |    | 105 |    | 110 |     |
| Ile Ala Asn Met Tyr Ser Leu His Ser Trp Val Gly Leu Ile Ala Val | 115 |    | 120 |    | 125 |     |
| Ile Cys Tyr Leu Leu Gln Leu Leu Ser Gly Phe Ser Val Phe Leu Leu | 130 |    | 135 |    | 140 |     |
| Pro Trp Ala Pro Leu Ser Leu Arg Ala Phe Leu Met Pro Ile His Val | 145 |    | 150 |    | 155 | 160 |
| Tyr Ser Gly Ile Val Ile Phe Gly Thr Val Ile Ala Thr Ala Leu Met | 165 |    | 170 |    | 175 |     |
| Gly Leu Thr Glu Lys Leu Ile Phe Ser Leu Arg Asp Pro Ala Tyr Ser | 180 |    | 185 |    | 190 |     |
| Thr Phe Pro Pro Glu Gly Val Phe Val Asn Thr Leu Gly Leu Leu Ile | 195 |    | 200 |    | 205 |     |
| Leu Val Phe Gly Ala Leu Ile Phe Trp Ile Val Thr Arg Pro Gln Trp | 210 |    | 215 |    | 220 |     |
| Lys Arg Pro Lys Glu Pro Asn Ser Thr Ile Leu His Pro Asn Gly Gly | 225 |    | 230 |    | 235 | 240 |
| Thr Glu Gln Gly Ala Arg Gly Ser Met Pro Ala Tyr Ser Gly Asn Asn | 245 |    | 250 |    | 255 |     |
| Met Asp Lys Ser Asp Ser Glu Leu Asn Ser Glu Val Ala Ala Arg Lys | 260 |    | 265 |    | 270 |     |
| Arg Asn Leu Ala Leu Asp Glu Ala Gly Gln Arg Ser Thr Met         | 275 |    | 280 |    | 285 |     |

&lt;210&gt; 405

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

255

<221> SITE  
 <222> (83)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (103)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (110)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (121)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (123)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (126)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (134)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (154)  
 <223> Xaa equals stop translation  
  
 <400> 405  
 Met Thr Lys Ala Arg Leu Phe Arg Leu Trp Leu Val Leu Gly Ser Val  
   1                  5                  10                  15  
 Phe Met Ile Leu Leu Ile Ile Val Tyr Trp Asp Ser Ala Gly Ala Ala  
                   20                  25                  30  
 His Phe Tyr Leu His Thr Ser Phe Ser Arg Pro His Thr Gly Pro Pro  
           35                  40                  45  
 Leu Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu Thr Ala Asp Ser  
   50                  55                  60  
 Asp Val Asp Xaa Phe Leu Asp Xaa Phe Leu Ser Ala Gly Val Lys Gln  
   65                  70                  75                  80  
 Ser Asp Xaa Pro Arg Lys Glu Thr Glu Gln Pro Pro Ala Pro Gly Ser  
           85                  90                  95

256

Met Glu Glu Ser Val Arg Xaa Tyr Asp Trp Ser Pro Arg Xaa Ala Arg  
                   100                  105                  110

Arg Thr Gln Thr Arg Ala Gly Ser Xaa Arg Xaa Gly Gly Xaa Cys Cys  
                   115                  120                  125

Gly Ala Ser Ala Pro Xaa Pro Ala Trp Pro Ser Pro Pro Arg Ser Ala  
                   130                  135                  140

His Ser Thr Thr Ser Pro Thr Arg Ser Xaa  
                   145                  150

<210> 406  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens

<400> 406  
 Met Leu Leu Leu Ile Val Leu Val Ala Asn Ile Leu Ser Met Ser Asn  
           1                  5                  10                  15

Met Ser Asn Ala Val Val Ser Asp Leu His Ile Leu Val His Leu Ile  
                   20                  25                  30

Ser His Lys Ala Asn  
                   35

<210> 407  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 407  
 Met Cys Ile His Val Phe Met Ser Val Leu Trp Val Leu Phe Leu Leu  
           1                  5                  10                  15

Asn Pro Leu Cys Thr Gly Leu Trp Pro Leu Val Asn Cys Phe Ser Val  
                   20                  25                  30

Leu Arg His Ala Asp Trp Val Leu Gly Ala Asp Tyr Lys Gly Glu Glu  
           35                  40                  45

Leu Asn Arg His Gln Gly Pro Met Lys Pro Lys Asp  
           50                  55                  60

<210> 408  
 <211> 447  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (447)  
 <223> Xaa equals stop translation

257

&lt;400&gt; 408

Met Leu Leu Gly Leu Leu Met Ala Ala Cys Phe Thr Phe Cys Leu Ser  
 1 5 10 15  
 His Gln Asn Leu Lys Glu Phe Ala Leu Thr Asn Pro Glu Lys Ser Ser  
 20 25 30  
 Thr Lys Glu Thr Glu Arg Lys Glu Thr Lys Ala Glu Glu Glu Leu Asp  
 35 40 45  
 Ala Glu Val Leu Glu Val Phe His Pro Thr His Glu Trp Gln Ala Leu  
 50 55 60  
 Gln Pro Gly Gln Ala Val Pro Ala Gly Ser His Val Arg Leu Asn Leu  
 65 70 75 80  
 Gln Thr Gly Glu Arg Glu Ala Lys Leu Gln Tyr Glu Asp Lys Phe Arg  
 85 90 95  
 Asn Asn Leu Lys Gly Lys Arg Leu Asp Ile Asn Thr Asn Thr Tyr Thr  
 100 105 110  
 Ser Gln Asp Leu Lys Ser Ala Leu Ala Lys Phe Lys Glu Gly Ala Glu  
 115 120 125  
 Met Glu Ser Ser Lys Glu Asp Lys Ala Arg Gln Ala Glu Val Lys Arg  
 130 135 140  
 Leu Phe Arg Pro Ile Glu Glu Leu Lys Lys Asp Phe Asp Glu Leu Asn  
 145 150 155 160  
 Val Val Ile Glu Thr Asp Met Gln Ile Met Val Arg Leu Ile Asn Lys  
 165 170 175  
 Phe Asn Ser Ser Ser Ser Ser Leu Glu Glu Lys Ile Ala Ala Leu Phe  
 180 185 190  
 Asp Leu Glu Tyr Tyr Val His Gln Met Asp Asn Ala Gln Asp Leu Leu  
 195 200 205  
 Ser Phe Gly Gly Leu Gln Val Val Ile Asn Gly Leu Asn Ser Thr Glu  
 210 215 220  
 Pro Leu Val Lys Glu Tyr Ala Ala Phe Val Leu Gly Ala Ala Phe Ser  
 225 230 235 240  
 Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly Ala Leu Gln  
 245 250 255  
 Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr Ala Lys Lys  
 260 265 270  
 Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe Pro Tyr Ala  
 275 280 285  
 Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu Arg Thr Leu  
 290 295 300

258

Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val Val Thr Leu  
 305 310 315 320  
 Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu Glu Ala Glu  
 325 330 335  
 Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr Arg Gln Val  
 340 345 350  
 His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu Ile Thr Ala  
 355 360 365  
 His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys Val Leu Gln  
 370 375 380  
 Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr Arg Gln Asp  
 385 390 395 400  
 Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu Tyr Gln Val  
 405 410 415  
 Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly Tyr Phe Gln  
 420 425 430  
 Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu Arg Xaa  
 435 440 445

&lt;210&gt; 409

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 409

Met Leu Tyr Ser Asp Leu Lys Leu Val Arg Cys His Asn Gly Pro Val  
 1 5 10 15  
 His Val Ile Ser Val Tyr Thr Thr Pro Pro Asp Pro Ser Asn Pro Tyr  
 20 25 30  
 Asn Thr Pro Pro Leu Phe Ala Ser Cys Met Val Ile Ser Tyr Val Thr  
 35 40 45  
 Phe Thr Pro Val Ser Ala Asp Cys Phe Phe Asn Val Leu Val Cys Phe  
 50 55 60

&lt;210&gt; 410

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (24)



259

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 410

Glu Leu Leu Phe Leu Leu Ile Ile Ile Leu Gly Glu Ser Leu Ser Asp  
1 5 10 15

Val Ile Leu Leu Ile Cys Phe Xaa  
20

&lt;210&gt; 411

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 411

Met Phe Tyr Trp Gly Gly Leu Ser Phe Tyr Phe Leu Leu Ser Ser Gly  
1 5 10 15

Val Gly Phe Tyr Cys Phe Leu Phe Gly Phe Gly Met Glu Ile Trp Ile  
20 25 30

Ala Ala Xaa  
35

&lt;210&gt; 412

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 412

Met Gly Lys Val Gly Trp Leu Met Val Gly Gly Val Ala Pro Gly Ile  
1 5 10 15

Arg Gly Gly Trp Gly Trp Thr Leu Gly Ile Met Val Gly Gly Ala Ile  
20 25 30

Ala His Cys Cys Cys Cys Leu Ile Arg  
35 40

&lt;210&gt; 413

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 413

260

Met Lys Leu Ser Leu Leu Ile Leu Thr Leu Met Gln Arg Tyr Phe Arg  
 1 5 10 15

Thr Ile Thr Asn Ser Leu Cys Lys Xaa  
 20 25

<210> 414  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (79)  
 <223> Xaa equals stop translation

<400> 414  
 Met Pro Ala Val Ser Gly Pro Gly Pro Leu Phe Cys Leu Leu Leu Leu  
 1 5 10 15

Leu Leu Asp Pro His Ser Pro Glu Thr Gly Cys Pro Pro Leu Arg Arg  
 20 25 30

Phe Glu Tyr Lys Leu Ser Phe Lys Gly Pro Arg Leu Ala Leu Pro Gly  
 35 40 45

Ala Gly Ile Pro Phe Trp Ser His His Gly Gly Glu Gly Gln Gly Trp  
 50 55 60

Gly Pro Leu Cys Pro Gly Ser Leu Lys Val Leu Glu Gly Leu Xaa  
 65 70 75

<210> 415  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (20)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (28)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 415  
 Met His Tyr Leu Leu Lys Glu Cys Asp Ile Asp Thr Asp Ala Tyr Phe  
 1 5 10 15

Phe Phe Phe Xaa Leu Leu Val Leu Phe Leu Pro Xaa Lys Tyr Ser Pro  
 20 25 30

Pro Phe Tyr Ser Ile Val Leu Phe Arg Trp Asn Asp Ser Tyr Lys Ile  
 35 40 45

261

Ser His Tyr  
50

&lt;210&gt; 416

&lt;211&gt; 257

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (100)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 416

Met Ala Ala Leu Thr Ser His Leu Gln Asn Gln Ser Asn Asn Ser Asn  
1 5 10 15

Trp Asn Leu Arg Thr Arg Ser Lys Cys Lys Lys Asp Val Phe Met Pro  
20 25 30

Pro Ser Ser Ser Ser Glu Leu Gln Glu Ser Arg Gly Leu Ser Asn Phe  
35 40 45

Thr Ser Thr His Leu Leu Leu Lys Glu Asp Glu Gly Val Asp Asp Val  
50 55 60

Asn Phe Arg Lys Val Arg Lys Pro Lys Gly Lys Val Thr Ile Leu Lys  
65 70 75 80

Gly Ile Pro Ile Lys Lys Thr Lys Lys Gly Cys Arg Lys Ser Cys Ser  
85 90 95

Gly Phe Val Xaa Ser Asp Ser Lys Arg Glu Ser Val Cys Asn Lys Ala  
100 105 110

Asp Ala Glu Ser Glu Pro Val Ala Gln Lys Ser Gln Leu Asp Arg Thr  
115 120 125

Val Cys Ile Ser Asp Ala Gly Ala Cys Gly Glu Thr Leu Ser Val Thr  
130 135 140

Ser Glu Glu Asn Ser Leu Val Lys Lys Lys Glu Arg Ser Leu Ser Ser  
145 150 155 160

Gly Ser Asn Phe Cys Ser Glu Gln Lys Thr Ser Gly Ile Ile Asn Lys  
165 170 175

Phe Cys Ser Ala Lys Asp Ser Glu His Asn Glu Lys Tyr Glu Asp Thr  
180 185 190

Phe Leu Glu Ser Glu Glu Ile Gly Thr Lys Val Glu Val Val Glu Arg  
195 200 205

Lys Glu His Leu His Thr Asp Ile Leu Lys Arg Gly Ser Glu Met Asp  
210 215 220

262

Asn Asn Cys Ser Pro Thr Arg Lys Asp Phe Thr Glu Asp Thr Ile Pro  
 225 230 235 240

Arg Asn Thr Asp Arg Lys Lys Glu Asn Lys Pro Val Phe Phe Gln Gln  
 245 250 255

Ile

&lt;210&gt; 417

&lt;211&gt; 424

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (144)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (263)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 417

Met Glu Lys Gln Cys Cys Ser His Pro Val Ile Cys Ser Leu Ser Thr  
 1 5 10 15

Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Ser  
 20 25 30

Arg Ile Leu Leu Val Lys Tyr Ser Ala Asn Glu Glu Asn Lys Tyr Asp  
 35 40 45

Tyr Leu Pro Thr Thr Val Asn Val Cys Ser Glu Leu Val Lys Leu Val  
 50 55 60

Phe Cys Val Leu Val Ser Phe Cys Val Ile Lys Lys Asp His Gln Ser  
 65 70 75 80

Arg Asn Leu Lys Tyr Ala Ser Trp Lys Glu Phe Ser Asp Phe Met Lys  
 85 90 95

Trp Ser Ile Pro Ala Phe Leu Tyr Phe Leu Asp Asn Leu Ile Val Phe  
 100 105 110

Tyr Val Leu Ser Tyr Leu Gln Pro Ala Met Ala Val Ile Phe Ser Asn  
 115 120 125

Phe Ser Ile Ile Thr Thr Ala Leu Leu Phe Arg Ile Val Leu Lys Xaa  
 130 135 140

Arg Leu Asn Trp Ile Gln Trp Ala Ser Leu Leu Thr Leu Phe Leu Ser  
 145 150 155 160

Ile Val Ala Leu Thr Ala Gly Thr Lys Thr Leu Gln His Asn Leu Ala  
 165 170 175

263

Gly Arg Gly Phe His His Asp Ala Phe Phe Ser Pro Ser Asn Ser Cys  
 180 185 190  
 Leu Leu Phe Arg Asn Glu Cys Pro Arg Lys Asp Asn Cys Thr Ala Lys  
 195 200 205  
 Glu Trp Thr Phe Pro Glu Ala Lys Trp Asn Thr Thr Ala Arg Val Phe  
 210 215 220  
 Ser His Ile Arg Leu Gly Met Gly His Val Leu Ile Ile Val Gln Cys  
 225 230 235 240  
 Phe Ile Ser Ser Met Ala Asn Ile Tyr Asn Glu Lys Ile Leu Lys Glu  
 245 250 255  
 Gly Asn Gln Leu Thr Glu Xaa Ile Phe Ile Gln Asn Ser Lys Leu Tyr  
 260 265 270  
 Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg Ser  
 275 280 285  
 Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe Tyr Gly His Ser Ala  
 290 295 300  
 Phe Ser Val Ala Leu Ile Phe Val Thr Ala Phe Gln Gly Leu Ser Val  
 305 310 315 320  
 Ala Phe Ile Leu Lys Phe Leu Asp Asn Met Phe His Val Leu Met Ala  
 325 330 335  
 Gln Val Thr Thr Val Ile Ile Thr Thr Val Ser Val Leu Val Phe Asp  
 340 345 350  
 Phe Arg Pro Ser Leu Glu Phe Phe Leu Glu Ala Pro Ser Val Leu Leu  
 355 360 365  
 Ser Ile Phe Ile Tyr Asn Ala Ser Lys Pro Gln Val Pro Glu Tyr Ala  
 370 375 380  
 Pro Arg Gln Glu Arg Ile Arg Asp Leu Ser Gly Asn Leu Trp Glu Arg  
 385 390 395 400  
 Ser Ser Gly Asp Gly Glu Glu Leu Glu Arg Leu Thr Lys Pro Lys Ser  
 405 410 415  
 Asp Glu Ser Asp Glu Asp Thr Phe  
 420

&lt;210&gt; 418

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

264

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 418

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Trp | Gly | Gln | Gly | Ser | Gln | Lys | Ser | His | Phe | Ser | Asp | Leu | Val | Phe |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Val | Arg | Glu | Leu | Cys | Ala | Gln | Pro | Ser | Asp | Pro | Gly | Ser | Pro | His |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |

Xaa

&lt;210&gt; 419

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 419

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Gln | His | Ile | Gln | Pro | Ala | Ala | Leu | Ser | Leu | Leu | Ala | Gln | Trp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     | 15  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Thr | Leu | Val | Gln | Glu | Leu | Glu | Ala | Ala | Leu | Gln | Leu | Ala | Phe | Tyr |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Asp | Ala | Val | Glu | Glu | Trp | Leu | Glu | Glu | Asn | Val | His | Pro | Ser | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Arg | Leu | Gln | Xaa | Leu | Leu | Gln | Asp | Leu | Ser | Glu | Val | Ser | Ala | Pro |
|     | 50  |     |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Leu | Pro | Pro | Thr | Ser | Pro | Gly | Arg | Asp | Val | Ala | Gln | Asp | Pro | Xaa |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |

&lt;210&gt; 420

&lt;211&gt; 95

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

265

<220>  
 <221> SITE  
 <222> (83)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (95)  
 <223> Xaa equals stop translation

<400> 420  
 Met Leu Asn Gln Gly Tyr Ile Arg Lys Ile Ile Leu Ile Ile Ile Leu  
 1 5 10 15  
 Gly Ser Phe Ser Ser Pro Lys Lys Ala Ile Leu Met Gly Phe Gln Asn  
 20 25 30  
 Gln Lys Lys Ala Leu Asn Glu Glu Gln Thr Thr Gly Val Pro Met Ser  
 35 40 45  
 Ile Ser Gly Lys Leu Arg Pro Ser Arg Ser Leu Asp Phe Val Gln Pro  
 50 55 60  
 Pro Arg Phe Gln Ser Gln Gln Pro Ser Ala Val Val Asp Arg Arg Gly  
 65 70 75 80  
 Phe Xaa Xaa Lys Ala Ala Arg Gly Gln Glu Phe Ser Glu Ser Xaa  
 85 90 95

<210> 421  
 <211> 257  
 <212> PRT  
 <213> Homo sapiens

<400> 421  
 Met Arg Gly Pro Ala Gln Ala Lys Leu Leu Pro Gly Ser Ala Ile Gln  
 1 5 10 15  
 Ala Leu Val Gly Leu Ala Arg Pro Leu Val Leu Ala Leu Leu Val  
 20 25 30  
 Ser Ala Ala Leu Ser Ser Val Val Ser Arg Thr Asp Ser Pro Ser Pro  
 35 40 45  
 Thr Val Leu Asn Ser His Ile Ser Thr Pro Asn Val Asn Ala Leu Thr  
 50 55 60  
 His Glu Asn Gln Thr Lys Pro Ser Ile Ser Gln Ile Ser Thr Thr Leu  
 65 70 75 80  
 Pro Pro Thr Thr Ser Thr Lys Lys Ser Gly Gly Ala Ser Val Val Pro  
 85 90 95  
 His Pro Ser Pro Thr Pro Leu Ser Gln Glu Glu Ala Asp Asn Asn Glu  
 100 105 110  
 Asp Pro Ser Ile Glu Glu Glu Asp Leu Leu Met Leu Asn Ser Ser Pro

266

115                      120                      125  
 Ser Thr Ala Lys Asp Thr Leu Asp Asn Gly Asp Tyr Gly Glu Pro Asp  
     130                      135                      140  
 Tyr Asp Trp Thr Thr Gly Pro Arg Asp Asp Asp Glu Ser Asp Asp Thr  
     145                      150                      155                      160  
 Leu Glu Glu Asn Arg Gly Tyr Met Glu Ile Glu Gln Ser Val Lys Ser  
                     165                      170                      175  
 Phe Lys Met Pro Ser Ser Asn Ile Glu Glu Glu Asp Ser His Phe Phe  
                     180                      185                      190  
 Phe His Leu Ile Ile Phe Ala Phe Cys Ile Ala Val Val Tyr Ile Thr  
                     195                      200                      205  
 Tyr His Asn Lys Arg Lys Ile Phe Leu Leu Val Gln Ser Arg Lys Trp  
                     210                      215                      220  
 Arg Asp Gly Leu Cys Ser Lys Thr Val Glu Tyr His Arg Leu Asp Gln  
     225                      230                      235                      240  
 Asn Val Asn Glu Ala Met Pro Ser Leu Lys Ile Thr Asn Asp Tyr Ile  
                     245                      250                      255

Phe

<210> 422  
 <211> 704  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 422

Met Trp Tyr Arg Leu Arg Leu Leu Lys Pro Gln Pro Asn Ile Ile Pro  
     1                      5                      10                      15  
 Thr Val Lys Lys Ile Val Leu Leu Ala Gly Trp Ala Leu Phe Leu Phe  
                     20                      25                      30  
 Leu Ala Tyr Lys Val Ser Lys Thr Asp Arg Glu Tyr Gln Glu Tyr Asn  
                     35                      40                      45  
 Pro Tyr Glu Val Leu Asn Leu Asp Pro Gly Ala Thr Val Ala Glu Ile  
                     50                      55                      60  
 Lys Lys Gln Tyr Arg Leu Leu Ser Leu Lys Tyr His Pro Asp Lys Gly  
     65                      70                      75                      80  
 Gly Asp Glu Val Met Phe Met Arg Ile Ala Lys Ala Tyr Ala Ala Leu  
                     85                      90                      95  
 Thr Asp Glu Glu Ser Arg Lys Asn Trp Glu Glu Phe Gly Asn Pro Asp  
                     100                      105                      110  
 Gly Pro Gln Ala Thr Ser Phe Gly Ile Ala Leu Pro Ala Trp Ile Val



267

| 115  | 120 | 125 |
|--|-----|-----|
| Asp Gln Lys Asn Ser Ile Leu Val Leu Leu Val Tyr Gly Leu Ala Phe<br>130 135 140     |     |     |
| Met Val Ile Leu Pro Val Val Val Gly Ser Trp Trp Tyr Arg Ser Ile<br>145 150 155 160 |     |     |
| Arg Tyr Ser Gly Asp Gln Ile Leu Ile Arg Thr Thr Gln Ile Tyr Thr<br>165 170 175     |     |     |
| Tyr Phe Val Tyr Lys Thr Arg Asn Met Asp Met Lys Arg Leu Ile Met<br>180 185 190     |     |     |
| Val Leu Ala Gly Ala Ser Glu Phe Asp Pro Gln Tyr Asn Lys Asp Ala<br>195 200 205     |     |     |
| Thr Ser Arg Pro Thr Asp Asn Ile Leu Ile Pro Gln Leu Ile Arg Glu<br>210 215 220     |     |     |
| Ile Gly Ser Ile Asn Leu Lys Lys Asn Glu Pro Pro Leu Thr Cys Pro<br>225 230 235 240 |     |     |
| Tyr Ser Leu Lys Ala Arg Val Leu Leu Leu Ser His Leu Ala Arg Met<br>245 250 255     |     |     |
| Lys Ile Pro Glu Thr Leu Glu Glu Asp Gln Gln Phe Met Leu Lys Lys<br>260 265 270     |     |     |
| Cys Pro Ala Leu Leu Gln Glu Met Val Asn Val Ile Cys Gln Leu Ile<br>275 280 285     |     |     |
| Val Met Ala Arg Asn Arg Glu Glu Arg Glu Phe Arg Ala Pro Thr Leu<br>290 295 300     |     |     |
| Ala Ser Leu Glu Asn Cys Met Lys Leu Ser Gln Met Ala Val Gln Gly<br>305 310 315 320 |     |     |
| Leu Gln Gln Phe Lys Ser Pro Leu Leu Gln Leu Pro His Ile Glu Glu<br>325 330 335     |     |     |
| Asp Asn Leu Arg Arg Val Ser Asn His Lys Lys Tyr Lys Ile Lys Thr<br>340 345 350     |     |     |
| Ile Gln Asp Leu Val Ser Leu Lys Glu Ser Asp Arg His Thr Leu Leu<br>355 360 365     |     |     |
| His Phe Leu Glu Asp Glu Lys Tyr Glu Glu Val Met Ala Val Leu Gly<br>370 375 380     |     |     |
| Ser Phe Pro Tyr Val Thr Met Asp Ile Lys Ser Gln Val Leu Asp Asp<br>385 390 395 400 |     |     |
| Glu Asp Ser Asn Asn Ile Thr Val Gly Ser Leu Val Thr Val Leu Val<br>405 410 415     |     |     |
| Lys Leu Thr Arg Gln Thr Met Ala Glu Val Phe Glu Lys Glu Gln Ser<br>420 425 430     |     |     |

268

Ile Cys Ala Ala Glu Glu Gln Pro Ala Glu Asp Gly Gln Gly Glu Thr  
 435 440 445  
 Asn Lys Asn Arg Thr Lys Gly Gly Trp Gln Gln Lys Ser Lys Gly Pro  
 450 455 460  
 Lys Lys Thr Ala Lys Ser Lys Lys Lys Lys Pro Leu Lys Lys Lys Pro  
 465 470 475 480  
 Thr Pro Val Leu Leu Pro Gln Ser Lys Gln Gln Lys Gln Lys Gln Ala  
 485 490 495  
 Asn Gly Val Val Gly Asn Glu Ala Ala Val Lys Glu Asp Glu Glu Glu  
 500 505 510  
 Val Ser Asp Lys Gly Ser Asp Ser Glu Glu Glu Glu Thr Asn Arg Asp  
 515 520 525  
 Ser Gln Ser Glu Lys Asp Asp Gly Ser Asp Arg Asp Ser Asp Arg Glu  
 530 535 540  
 Gln Asp Glu Lys Gln Asn Lys Asp Asp Glu Ala Glu Trp Gln Glu Leu  
 545 550 555 560  
 Gln Gln Ser Ile Gln Arg Lys Glu Arg Ala Leu Leu Glu Thr Lys Ser  
 565 570 575  
 Lys Ile Thr His Pro Val Tyr Ser Leu Tyr Phe Pro Glu Glu Lys Gln  
 580 585 590  
 Glu Trp Trp Trp Leu Tyr Ile Ala Asp Arg Lys Glu Gln Thr Leu Ile  
 595 600 605  
 Ser Met Pro Tyr His Val Cys Thr Leu Lys Asp Thr Glu Glu Val Glu  
 610 615 620  
 Leu Lys Phe Pro Ala Pro Gly Lys Pro Gly Asn Tyr Gln Tyr Thr Val  
 625 630 635 640  
 Phe Leu Arg Ser Asp Ser Tyr Met Gly Leu Asp Gln Ile Lys Pro Leu  
 645 650 655  
 Lys Leu Glu Val His Glu Ala Lys Pro Val Pro Glu Asn His Pro Gln  
 660 665 670  
 Trp Asp Thr Ala Ile Glu Gly Asp Glu Asp Gln Glu Asp Ser Glu Gly  
 675 680 685  
 Phe Glu Asp Ser Phe Glu Glu Glu Glu Glu Glu Glu Asp Asp Asp  
 690 695 700

&lt;210&gt; 423

&lt;211&gt; 190

269

<212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 423  
 Met Lys Ala Ser Gln Cys Cys Cys Cys Leu Ser His Leu Leu Ala Ser  
           1                  5                  10                  15  
 Val Leu Leu Leu Leu Leu Leu Pro Glu Leu Ser Gly Xaa Leu Xaa Val  
                   20                  25                  30  
 Leu Leu Gln Ala Ala Glu Ala Ala Pro Gly Leu Gly Pro Pro Asp Pro  
           35                  40                  45  
 Arg Pro Arg Thr Leu Pro Pro Leu Pro Pro Gly Pro Thr Pro Ala Gln  
           50                  55                  60  
 Gln Pro Gly Arg Gly Leu Ala Glu Ala Ala Gly Pro Arg Gly Ser Glu  
           65                  70                  75                  80  
 Gly Gly Asn Gly Ser Asn Pro Val Ala Gly Leu Glu Thr Asp Asp His  
                   85                  90                  95  
 Gly Gly Lys Ala Gly Glu Gly Ser Val Gly Gly Gly Leu Ala Val Ser  
           100                  105                  110  
 Pro Asn Pro Gly Asp Lys Pro Met Thr Gln Arg Ala Leu Thr Val Leu  
           115                  120                  125  
 Met Val Val Ser Gly Ala Val Leu Val Tyr Phe Val Val Arg Thr Val  
           130                  135                  140  
 Arg Met Arg Arg Arg Asn Arg Lys Thr Arg Arg Tyr Gly Val Leu Asp  
           145                  150                  155                  160  
 Thr Asn Ile Glu Asn Met Glu Leu Thr Pro Leu Glu Gln Asp Asp Glu  
                   165                  170                  175  
 Asp Asp Asp Asn Thr Leu Phe Asp Ala Asn His Pro Arg Arg  
           180                  185                  190

<210> 424  
 <211> 179  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE

270

&lt;222&gt; (179)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 424

Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile  
 1 5 10 15

Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser  
 20 25 30

Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp  
 35 40 45

Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro  
 50 55 60

Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly  
 65 70 75 80

Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Lys Ser Thr Lys  
 85 90 95

Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser  
 100 105 110

Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly  
 115 120 125

Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys  
 130 135 140

Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile  
 145 150 155 160

Leu Thr Ser Gly Lys Cys Arg Gln Leu Ser Arg Leu Cys Arg Asn His  
 165 170 175

Cys Arg Xaa

&lt;210&gt; 425

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 425

Met Phe Lys Cys Leu Gln Thr Thr Phe Leu Phe Ile Leu Asp Phe Thr  
 1 5 10 15

Trp Glu Ser Lys Val Gln Phe His Lys Ala Ser Val Tyr Leu Ser Leu  
 20 25 30

Ser Ile Tyr Ile Asp Cys His Ala  
 35 40

&lt;210&gt; 426

271

&lt;211&gt; 232

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 426

Met Leu Ala Gly Lys Leu Ile Pro Val His Gln Val Arg Gly Leu Lys  
 1 5 10 15  
 Glu Lys Ile Val Arg Ser Phe Glu Val Ser Pro Asp Gly Ser Phe Leu  
 20 25 30  
 Leu Ile Asn Gly Ile Ala Gly Tyr Leu His Leu Leu Ala Met Lys Thr  
 35 40 45  
 Lys Glu Leu Ile Gly Ser Met Lys Ile Asn Gly Arg Val Ala Ala Ser  
 50 55 60  
 Thr Phe Ser Ser Asp Ser Lys Lys Val Tyr Ala Ser Ser Gly Asp Gly  
 65 70 75 80  
 Glu Val Tyr Val Trp Asp Val Asn Ser Arg Lys Cys Leu Asn Arg Phe  
 85 90 95  
 Val Asp Glu Gly Ser Leu Tyr Gly Leu Ser Ile Ala Thr Ser Arg Asn  
 100 105 110  
 Gly Gln Tyr Val Ala Cys Gly Ser Asn Cys Gly Val Val Asn Ile Tyr  
 115 120 125  
 Asn Gln Asp Ser Cys Leu Gln Glu Thr Asn Pro Lys Pro Ile Lys Ala  
 130 135 140  
 Ile Met Asn Leu Val Thr Gly Val Thr Ser Leu Thr Phe Asn Pro Thr  
 145 150 155 160  
 Thr Glu Ile Leu Ala Ile Ala Ser Glu Lys Met Lys Glu Ala Val Arg  
 165 170 175  
 Leu Val His Leu Pro Ser Cys Thr Val Phe Ser Asn Phe Pro Val Ile  
 180 185 190  
 Lys Asn Lys Asn Ile Ser His Val His Thr Met Asp Phe Ser Pro Arg  
 195 200 205  
 Ser Gly Tyr Phe Ala Leu Gly Asn Glu Lys Gly Lys Ala Leu Met Tyr  
 210 215 220  
 Arg Leu His His Tyr Ser Asp Phe  
 225 230

&lt;210&gt; 427

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 427

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val

272

1                      5                      10                      15  
 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser  
                             20                      25                      30  
 Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly  
                             35                      40                      45  
 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu  
                             50                      55                      60  
 Lys Pro Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu  
                             65                      70                      75                      80  
 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro  
                             85                      90                      95  
 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met  
                             100                      105                      110  
 Leu Val Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro  
                             115                      120                      125  
 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile  
                             130                      135                      140  
 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr  
                             145                      150                      155                      160  
 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn  
                             165                      170                      175  
 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln  
                             180                      185                      190  
 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val  
                             195                      200                      205  
 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys  
                             210                      215                      220  
 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val  
                             225                      230                      235                      240  
 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn  
                             245                      250

&lt;210&gt; 428

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 428

Met Trp Thr Lys Asn Asp Lys Leu Lys Lys Phe Phe Phe Leu Arg Tyr  
 1                      5                      10                      15

Leu Gln Asn Met Val Tyr Phe Tyr Val Glu Lys Lys Ser Tyr Glu Gly

273

|   |    |  |    |  |    |
|---|----|--|----|--|----|
|   | 20 |  | 25 |  | 30 |
| Ser Cys Tyr Phe Lys Arg Lys Phe Ile Lys Ser Pro Arg Gly Met Lys |    |  |    |  |    |
|   | 35 |  | 40 |  | 45 |
| Met Thr Ala Cys Phe Ser Ile Ile Leu Ala                         |    |  |    |  |    |
|   | 50 |  | 55 |  |    |

<210> 429  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (105)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (117)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (219)  
 <223> Xaa equals stop translation

|   |
|---|
| <400> 429   |
| Met Ala Val Val Leu Leu Ala Asn Leu Ala Gln Gly Asp Ser Leu Ala |
| 1 5 10 15   |

|   |
|---|
| Ala Arg Ala Ile Ala Val Gln Lys Gly Ser Ile Gly Asn Leu Leu Gly |
| 20 25 30  |

|   |
|---|
| Phe Leu Glu Asp Ser Leu Ala Ala Thr Gln Phe Gln Gln Ser Gln Ala |
| 35 40 45  |

|   |
|---|
| Ser Leu Leu His Met Gln Asn Pro Pro Phe Glu Pro Xaa Ser Val Asp |
| 50 55 60  |

|   |
|---|
| Met Met Arg Arg Ala Ala Arg Ala Leu Leu Ala Leu Ala Lys Val Asp |
| 65 70 75 80   |

|   |
|---|
| Glu Asn His Ser Glu Phe Thr Leu Tyr Glu Ser Arg Leu Leu Asp Ile |
| 85 90 95  |

|   |
|---|
| Ser Val Ser Pro Leu Met Asn Ser Xaa Val Ser Gln Val Ile Cys Asp |
| 100 105 110   |

|   |
|---|
| Val Leu Phe Leu Xaa Trp Pro Val Met Thr Ala Val Gly His Leu Pro |
| 115 120 125   |

274

Pro Pro Cys Val Cys Ala Cys Val Glu Asn Leu Glu Thr Asp Cys Cys  
 130 135 140

Pro Leu Phe Met Gln Asn His Leu Arg Ile Gln Phe Thr Leu Cys Cys  
 145 150 155 160

Pro Ala Ser Pro Leu Gly Lys Ser Leu Ser Cys Phe Ser Leu Leu Leu  
 165 170 175

Pro Pro Pro Leu Pro Pro Ser Pro His Ala Phe Leu Phe Leu Val Leu  
 180 185 190

Thr Leu Leu Pro Ser Gly Pro Tyr Pro Thr Leu Phe Glu Lys Thr Lys  
 195 200 205

Leu Cys Leu His Arg Arg Leu Phe Leu Phe Xaa  
 210 215

&lt;210&gt; 430

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 430

Met Leu Pro Asp Glu Ser Phe Gly Leu Leu Leu Ser Ile Pro Ser Leu  
 1 5 10 15

Thr Pro Ser Ala Ala Ala Pro Ser Phe Cys Val His Leu Met Gln Ala  
 20 25 30

Ser Arg Ser Ser Lys Arg Ala Ser His Val Pro Val His Leu Leu Trp  
 35 40 45

Gly Asp Xaa  
 50

&lt;210&gt; 431

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation



275

&lt;400&gt; 431

Met Arg Pro Gly Ser Phe Ser Phe Ile Ala Phe Leu Ala Thr Glu Val  
 1 5 10 15  
 Ser Ser Cys Phe Pro Gly Arg Pro Asp Cys Xaa Thr Gly Met Trp Leu  
 20 25 30  
 Leu Gln Leu Gln Lys Lys Gln Arg Thr Leu Leu Ala Met Ala Pro Arg  
 35 40 45  
 Arg Xaa  
 50

&lt;210&gt; 432

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (39)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 432

Asp Arg Pro Cys Pro Ser Ser Leu Trp Lys Val Phe Pro Leu Leu Leu  
 1 5 10 15  
 Leu Leu Met Arg Leu Phe Pro Leu Pro Val Pro Gly Asn Gln Arg Ala  
 20 25 30  
 Xaa Leu Pro His Pro Phe Xaa Ala Pro Arg Leu Pro Cys Leu Leu Cys  
 35 40 45  
 Leu Cys Thr Gln Gln Phe Xaa Val Cys Ser His Tyr Leu Pro Ala Gly  
 50 55 60  
 Tyr Arg Val Asn Ser Xaa  
 65 70

&lt;210&gt; 433

276

<211> 40  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (40)  
<223> Xaa equals stop translation

<400> 433  
Met His Glu Lys Ala Trp Asn Leu Ile Leu Leu Trp Trp Leu Ser Leu  
1 5 10 15  
Asp Leu Leu Gly Val Ala Lys Thr Ala Met Trp Ala Gln Trp Cys Gly  
20 25 30  
Leu Asn Asp His Lys Gly Lys Xaa  
35 40

<210> 434  
<211> 104  
<212> PRT  
<213> Homo sapiens

<400> 434  
Met Ala Phe Val Leu Leu Phe Cys Phe Val Gly Leu Gln Ser Ser Arg  
1 5 10 15  
Ala Gly Pro Tyr Ser Glu Leu Val Leu Cys Gln Thr Pro Ala Ser Ala  
20 25 30  
Pro Asp Pro Val Ser Thr Leu Cys Val Leu Glu Glu Glu Pro Leu Asp  
35 40 45  
Ala Tyr Pro Asp Ser Pro Ser Ala Cys Leu Val Leu Asn Trp Glu Glu  
50 55 60  
Pro Cys Asn Asn Gly Ser Glu Ile Leu Ala Tyr Thr Ile Asp Leu Gly  
65 70 75 80  
Asp Thr Ser Ile Thr Val Gly Asn Thr Thr Met His Val Met Lys Asp  
85 90 95  
Leu Leu Pro Glu Thr Thr Tyr Arg  
100

<210> 435  
<211> 38  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (38)  
<223> Xaa equals stop translation

277

&lt;400&gt; 435

Met Phe Ser Leu Leu Trp Leu Val Cys Val Pro Ser Asn Ser Ser Val  
1 5 10 15

Ala Asn Val Thr Ala Ser Arg Gly Gly Val Phe Lys Arg Ser Leu Gly  
20 25 30

His Glu Gly Phe Ser Xaa  
35

&lt;210&gt; 436

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 436

Lys Trp Leu Leu Phe Ile Phe Leu Leu Cys Leu Gln Leu Val Asn Ala  
1 5 10 15

Leu Leu Ser Leu Phe Gln Glu Arg Phe Val His Cys Pro Ala Arg Phe  
20 25 30

Val Ser Xaa  
35

&lt;210&gt; 437

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (32)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 437

Met Leu Leu Phe Leu Ser Ile Thr Asn Ser Leu Ser Phe Ile Ser Val  
1 5 10 15

Asp Lys Pro Phe Gly Gln Ser Glu Asp Val Cys Pro Val Ile Ser Xaa  
20 25 30

&lt;210&gt; 438

&lt;211&gt; 127

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

278

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (127)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 438

Met Glu Phe Leu Phe Asn Lys Thr Gly Trp Ala Phe Ala Ala Leu Cys  
 1 5 10 15

Phe Val Leu Ala Met Thr Ser Gly Gln Met Trp Asn His Ile Arg Gly  
 20 25 30

Pro Pro Tyr Ala His Lys Asn Pro His Thr Gly His Val Asn Tyr Ile  
 35 40 45

His Gly Ser Ser Gln Ala Gln Phe Val Ala Glu Thr His Ile Val Leu  
 50 55 60

Leu Phe Asn Gly Gly Val Thr Leu Gly Met Val Leu Leu Cys Glu Ala  
 65 70 75 80

Ala Thr Ser Asp Met Asp Ile Gly Lys Arg Lys Ile Met Cys Val Ala  
 85 90 95

Gly Ile Gly Leu Val Val Leu Phe Phe Ser Trp Met Leu Ser Ile Phe  
 100 105 110

Arg Ser Lys Tyr His Gly Tyr Pro Tyr Ser Phe Leu Met Ser Xaa  
 115 120 125

&lt;210&gt; 439

&lt;211&gt; 69

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 439

Met Thr Trp His Ser Arg Glu Ser Phe Xaa Leu Leu Arg Val Val Ala  
 1 5 10 15

Pro Ser Gln Ala Pro Gly Met Gln Val Ser Pro Ser Gln Arg Ala Trp  
 20 25 30

Arg Arg Pro Leu His Arg Cys His Val Ala Ala Pro Arg Pro His His  
 35 40 45

Phe Ala Phe Phe Arg Asn Pro Phe Ser Trp Ser Phe Ile Lys Leu Leu  
 50 55 60

279

Tyr Arg Tyr Leu Xaa  
65

&lt;210&gt; 440

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 440

Met Gly Leu Lys Leu Asn Gly Arg Tyr Ile Ser Leu Ile Leu Ala Val  
1 5 10 15

Gln Ile Ala Tyr Leu Val Gln Ala Val Arg Ala Ala Gly Lys Cys Asp  
20 25 30

Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp Thr  
35 40 45

Trp Pro Thr Thr Arg Ser Leu Gly Arg Gln Asp Glu His Gln Asp Arg  
50 55 60

Val His Ile Leu Gly Gly Phe Pro Gln Leu His Gly His Ser Pro Tyr  
65 70 75 80

Gly Leu Pro Gly Arg Gly Glu Arg Tyr Val Gly Xaa  
85 90

&lt;210&gt; 441

&lt;211&gt; 380

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (264)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (296)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (380)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 441

Met Ala Arg Arg Ser Ala Phe Pro Ala Ala Ala Leu Trp Leu Trp Ser  
1 5 10 15

280

Ile Leu Leu Cys Leu Leu Ala Leu Arg Ala Glu Ala Gly Pro Pro Gln  
                   20                  25                  30  
 Glu Glu Ser Leu Tyr Leu Trp Ile Asp Ala His Gln Ala Arg Val Leu  
           35                  40                  45  
 Ile Gly Phe Glu Glu Asp Ile Leu Ile Val Ser Glu Gly Lys Met Ala  
       50                  55                  60  
 Pro Phe Thr His Asp Phe Arg Lys Ala Gln Gln Arg Met Pro Ala Ile  
       65                  70                  75                  80  
 Pro Val Asn Ile His Ser Met Asn Phe Thr Trp Gln Ala Ala Gly Gln  
                   85                  90                  95  
 Ala Glu Tyr Phe Tyr Glu Phe Leu Ser Leu Arg Ser Leu Asp Lys Gly  
           100                  105                  110  
 Ile Met Ala Asp Pro Thr Val Asn Val Pro Leu Leu Gly Thr Val Pro  
       115                  120                  125  
 His Lys Ala Ser Val Val Gln Val Gly Phe Pro Cys Leu Gly Lys Gln  
       130                  135                  140  
 Asp Gly Val Ala Ala Phe Glu Val Asp Val Ile Val Met Asn Ser Glu  
   145                  150                  155                  160  
 Gly Asn Thr Ile Leu Gln Thr Pro Gln Asn Ala Ile Phe Phe Lys Thr  
           165                  170                  175  
 Cys Gln Gln Ala Glu Cys Pro Gly Gly Cys Arg Asn Gly Gly Phe Cys  
           180                  185                  190  
 Asn Glu Arg Arg Ile Cys Glu Cys Pro Asp Gly Phe His Gly Pro His  
       195                  200                  205  
 Cys Glu Lys Ala Leu Cys Thr Pro Arg Cys Met Asn Gly Gly Leu Cys  
       210                  215                  220  
 Val Thr Pro Gly Phe Cys Ile Cys Pro Pro Gly Phe Tyr Gly Val Asn  
   225                  230                  235                  240  
 Cys Asp Lys Ala Asn Cys Ser Thr Thr Cys Phe Asn Gly Gly Thr Cys  
           245                  250                  255  
 Phe Tyr Pro Gly Lys Cys Ile Xaa Pro Pro Gly Leu Glu Gly Glu Gln  
       260                  265                  270  
 Cys Glu Ile Ser Lys Cys Pro Gln Pro Cys Arg Asn Gly Gly Lys Cys  
       275                  280                  285  
 Ile Gly Lys Ser Lys Cys Lys Xaa Ser Lys Gly Tyr Gln Gly Asp Leu  
       290                  295                  300  
 Cys Ser Lys Pro Val Cys Glu Pro Gly Cys Gly Ala His Gly Thr Cys  
   305                  310                  315                  320

281

His Glu Pro Asn Lys Cys Gln Cys Gln Glu Gly Trp His Gly Arg His  
                           325                          330                          335

Cys Asn Lys Arg Tyr Glu Ala Ser Leu Ile His Ala Leu Arg Pro Ala  
                           340                          345                          350

Gly Ala Gln Leu Arg Gln His Thr Pro Ser Leu Lys Lys Ala Glu Glu  
                           355                          360                          365

Arg Arg Asp Pro Pro Glu Ser Asn Tyr Ile Trp Xaa  
                           370                          375                          380

&lt;210&gt; 442

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (23)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (24)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 442

Met Thr Ser Asn Leu Leu Leu Thr Leu Leu Lys Asp Thr Leu  
       1                          5                          10                          15

Xaa Leu Ala Lys Xaa Asn Xaa Xaa  
                           20

&lt;210&gt; 443

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

282

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 443

Met Arg His His Thr Gln Leu Asn Phe Ile Phe Leu Val Glu Met Val  
 1 5 10 15

Phe Leu His Val Gly Gln Ala Gly Leu Lys Leu Pro Thr Ser Gly Asp  
 20 25 30

Xaa Ala Cys Phe Gly Leu Pro Lys Val Leu Gly Leu Gln Ala Xaa  
 35 40 45

&lt;210&gt; 444

&lt;211&gt; 214

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 444

Met Gln Val Thr Ile Thr Leu Thr Ser Pro Ile Ile Arg Glu Glu Asn  
 1 5 10 15

Met Arg Glu Gly Asp Val Thr Ser Gly Met Val Lys Asp Pro Pro Asp  
 20 25 30

Val Leu Asp Arg Gln Lys Cys Leu Asp Ala Leu Ala Ala Leu Arg His  
 35 40 45

Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Gln Ser Cys Val Ile  
 50 55 60

Ile Ile Arg Ile Leu Arg Asp Leu Cys Gln Arg Val Pro Thr Trp Ser  
 65 70 75 80

Asp Phe Pro Ser Trp Ala Met Glu Leu Leu Val Glu Lys Ala Ile Ser  
 85 90 95

Ser Ala Ser Ser Pro Gln Ser Pro Gly Asp Ala Leu Arg Arg Val Phe  
 100 105 110

Glu Cys Ile Ser Ser Gly Ile Ile Leu Lys Gly Ser Pro Gly Leu Leu  
 115 120 125

Asp Pro Cys Glu Lys Asp Pro Phe Asp Thr Leu Ala Thr Met Thr Asp  
 130 135 140

Gln Gln Arg Glu Asp Ile Thr Ser Ser Ala Gln Phe Ala Leu Arg Leu  
 145 150 155 160

Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro  
 165 170 175

Gln Met Ser Gln Arg Phe Asn Ile His Asn Asn Arg Lys Arg Arg Arg  
 180 185 190

Asp Ser Asp Gly Val Asp Gly Phe Glu Ala Glu Gly Lys Lys Asp Lys  
 195 200 205



283

Lys Asp Tyr Asp Asn Phe  
210

&lt;210&gt; 445

&lt;211&gt; 144

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (144)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 445

Leu Leu Ser Ile Leu Leu Cys Leu Leu Ala Ser Gly Leu Val Val Phe  
1 5 10 15

Phe Leu Phe Pro His Ser Val Leu Val Asp Asp Asp Gly Ile Lys Val  
20 25 30

Val Lys Val Thr Phe Asn Lys Gln Asp Ser Leu Val Ile Leu Thr Ile  
35 40 45

Met Ala Thr Leu Lys Ile Arg Asn Ser Asn Phe Tyr Thr Val Ala Val  
50 55 60

Thr Ser Leu Ser Ser Gln Ile Gln Tyr Met Asn Thr Val Val Asn Phe  
65 70 75 80

Thr Gly Lys Ala Glu Met Gly Gly Pro Phe Ser Tyr Val Tyr Phe Phe  
85 90 95

Cys Thr Val Pro Glu Ile Leu Val His Asn Ile Val Ile Phe Met Arg  
100 105 110

Thr Ser Val Lys Ile Ser Tyr Ile Gly Leu Met Thr Gln Ser Ser Leu  
115 120 125

Glu Thr His His Tyr Val Asp Cys Gly Gly Asn Ser Thr Ala Ile Xaa  
130 135 140

&lt;210&gt; 446

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 446

284

Met Phe Phe Phe Leu Tyr Val Tyr Ser Val Leu Cys Gly Leu Leu Val  
 1 5 10 15  
 Tyr Pro Ser Leu Pro Ser His Ser Val Ser Leu Val Thr Ser Leu Val  
 20 25 30  
 Ala Ser Ala Leu Xaa  
 35

<210> 447  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals stop translation

<400> 447  
 Met Ala Ser Ile Asn Ala Val Tyr Ile His Val Phe Leu Gly Val Cys  
 1 5 10 15  
 Val Gln Ala Thr Ala Ala Cys Pro Trp Cys Ser Gln Cys Arg Xaa Gly  
 20 25 30  
 Ser Val Pro Ser Xaa  
 35

<210> 448  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (192)  
 <223> Xaa equals stop translation

<400> 448  
 Met Met Ala Ala Met Val Leu Thr Ser Leu Ser Cys Ser Pro Val Val  
 1 5 10 15  
 Gln Ser Pro Pro Gly Thr Glu Ala Asn Phe Ser Ala Ser Arg Ala Ala  
 20 25 30

285

Cys Asp Pro Trp Lys Glu Ser Gly Asp Ile Ser Asp Ser Gly Xaa Ser  
           35                          40                          45  
 Thr Thr Ser Gly His Trp Ser Gly Ser Ser Gly Val Ser Thr Pro Ser  
           50                          55                          60  
 Pro Pro His Pro Gln Ala Ser Pro Lys Tyr Leu Gly Asp Ala Phe Gly  
           65                          70                          75                          80  
 Ser Pro Gln Thr Asp His Gly Phe Glu Thr Asp Pro Asp Pro Phe Leu  
                           85                          90                          95  
 Leu Asp Glu Pro Ala Pro Arg Lys Arg Lys Asn Ser Val Lys Val Met  
                   100                          105                          110  
 Tyr Lys Cys Leu Trp Pro Asn Cys Gly Lys Val Leu Arg Ser Ile Val  
           115                          120                          125  
 Gly Ile Lys Arg His Val Lys Ala Leu His Leu Gly Asp Thr Val Asp  
           130                          135                          140  
 Ser Asp Gln Phe Lys Arg Glu Glu Asp Phe Tyr Tyr Thr Glu Val Gln  
           145                          150                          155                          160  
 Leu Lys Glu Glu Ser Ala Ala Ala Ala Ala Ala Ala Ala Asp Pro  
                   165                          170                          175  
 Gln Ser Leu Gly Leu Pro Pro Pro Ser Gln Leu Pro Pro Pro Ala Xaa  
                   180                          185                          190

&lt;210&gt; 449

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 449

Met Ser Thr Asn Tyr Leu Thr Asp Val Cys Ser Leu Phe Ser Tyr Leu  
       1                          5                          10                          15

Asn Tyr Leu Tyr Phe His His His Leu Pro Val Pro Asn Thr Xaa  
           20                          25                          30

&lt;210&gt; 450

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

286

<221> SITE  
 <222> (44)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (77)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (78)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (101)  
 <223> Xaa equals stop translation  
  
 <400> 450  
 Met Gly Phe Phe Phe Val Leu Phe Phe Leu Tyr Leu Ala Leu Ser Arg  
   1                  5                  10                  15  
 Asp Trp Ser Ile Asn Phe Leu Lys Asp His Arg Ile Asn Phe Phe Val  
                   20                  25                  30  
 Ala Thr Ser Tyr Phe Ser Val Tyr Val Arg Gly Xaa Pro Xaa Val Pro  
           35                  40                  45  
 Ala Asp Thr Pro Leu Gly Pro Leu Leu Ser Leu Trp Leu His His Asn  
   50                  55                  60  
 Ala Phe Phe Ser Ile Leu Pro Lys Phe Pro Glu Asn Xaa Xaa Phe Leu  
   65                  70                  75                  80  
 Ile Leu Lys Lys Leu Val Val Glu Met Gly Trp Asp Leu Phe Ile Ser  
                   85                  90                  95  
 Pro Glu Asn Lys Xaa  
                   100

<210> 451  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals stop translation  
  
 <400> 451

287

Met Ala Arg Tyr Phe Ile Phe Phe Ile Leu Val Phe Met Lys Val Ser  
1 5 10 15  
Leu Asn Thr Thr Trp Pro Ala Pro Arg Pro Ala Thr Leu Arg Thr Ala  
20 25 30  
Asn Lys Ser Lys Xaa  
35

<210> 452  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

<400> 452  
Phe Ser Thr Ile Arg Ser Gly Leu Thr Asp Arg Ser Val Asn Phe Leu  
1 5 10 15  
Phe Leu Phe Leu Asp Val Pro Asp Cys Arg Leu Val Asn Ile Glu Leu  
20 25 30  
Met Ala Asn Ser Thr Val Thr His Ala Xaa  
35 40

<210> 453  
<211> 48  
<212> PRT  
<213> Homo sapiens

<400> 453  
Met Ser Glu Trp Glu Leu Ser Ser Lys Phe Ser Gln Thr Gln Arg Gln  
1 5 10 15  
His Cys Leu Leu Leu Asn Asp Tyr Ser Phe Leu Pro Val Phe Trp Tyr  
20 25 30  
Phe Leu Gly Ile Leu Leu Thr Thr Ala Ile Thr Leu Phe Tyr Phe His  
35 40 45

<210> 454  
<211> 25  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (25)

288

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 454

Met Pro Trp Arg Arg Ala Gly Leu Met Met Leu Pro Ile Ile Thr Gly  
1 5 10 15  
Cys Cys Pro Cys Ser Ala Ser Ile Xaa  
20 25

&lt;210&gt; 455

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 455

Met Tyr Leu Cys Lys Thr Val Lys Val Leu Ile Cys Tyr Asp Trp Ile  
1 5 10 15  
Leu Gly Leu Val Ser Ser Gly Gln His Trp Val Val Ser Leu Ser Tyr  
20 25 30  
Ser Ile Arg Val Tyr Pro Ala Met His Phe Thr Leu Cys Val His Ile  
35 40 45  
Tyr Ser Lys Glu Pro Cys  
50

&lt;210&gt; 456

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 456

Met Thr Ala Leu Val Trp Arg Lys Gly Pro Asp Gly Gly Ser Arg Lys  
1 5 10 15  
Pro Ile Leu Leu Leu Phe Phe Phe Leu Pro Leu Ile Leu Cys Phe His  
20 25 30  
Ser Phe Ile His Ser Ser Asn Ile Cys Xaa  
35 40

&lt;210&gt; 457

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

289

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 457

Met Phe Leu Thr Thr Trp Phe Leu Leu Ser Val Ala Trp Xaa Ala  
 1 5 10 15

Leu Thr Arg Ser Gly Arg Ser Cys Leu Pro Leu Val Gly Arg Pro Arg  
 20 25 30

Glu Gln Ser Pro Arg Thr His Cys Ala Ala Ser Ser Thr Lys Glu Arg  
 35 40 45

Asn Ser Asp Pro Gln Pro Ser Pro Pro Glu Val Val Gly Pro Leu Trp  
 50 55 60

Ser Xaa  
 65

&lt;210&gt; 458

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 458

Met Lys Ala Ile Gly Ile Glu Pro Ser Leu Ala Thr Tyr His His Ile  
 1 5 10 15

Ile Arg Leu Phe Asp Gln Pro Gly Asp Pro Leu Lys Arg Ser Ser Phe  
 20 25 30

Ile Ile Tyr Asp Ile Met Asn Glu Leu Met Gly Lys Arg Phe Ser Pro  
 35 40 45

Lys Asp Pro Asp Asp Asp Lys Phe Phe Gln Ser Ala Met Ser Ile Cys  
 50 55 60

Ser Ser Leu Arg Asp Leu Glu Leu Ala Tyr Gln Val His Gly Leu Leu  
 65 70 75 80

Lys Thr Gly Asp Asn Trp Lys Phe Ile Gly Pro Asp Gln His Arg Asn  
 85 90 95

Phe Tyr Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile  
 100 105 110

Asp Val Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala Tyr Phe  
 115 120 125

Pro His Ser Gln Thr Met Ile His Leu Leu Gln Ala Leu Asp Val Ala  
 130 135 140

Asn Arg Leu Glu Val Ile Pro Lys Ile Trp Glu Arg

290

145

150

155

&lt;210&gt; 459

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 459

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asn | Asp | Asn | Ser | Pro | Asn | His | Ser | Ser | Ser | Tyr | Leu | Pro | Leu | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Thr | Ile | Val | Ile | Leu | Gln | Thr | Gly | His | Lys | Gly | Thr | Leu | Xaa |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |

&lt;210&gt; 460

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 460

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | His | Phe | Leu | Phe | Arg | Phe | Ile | Val | Phe | Phe | Tyr | Leu | Trp | Gly | Leu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Thr | Ala | Gln | Arg | Gln | Lys | Lys | Glu | Glu | Ser | Thr | Glu | Glu | Val | Lys |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Glu | Val | Leu | His | Arg | Pro | Glu | Asn | Cys | Ser | Lys | Thr | Ser | Lys | Lys |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Asp | Leu | Leu | Lys | Cys | Pro | Leu | Xaa |
|     | 50  |     |     |     |     | 55  |     |     |

&lt;210&gt; 461

&lt;211&gt; 416

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (338)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (416)



291

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 461

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro  
 1 5 10 15  
 Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys  
 20 25 30  
 Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
 35 40 45  
 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
 50 55 60  
 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp  
 65 70 75 80  
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr  
 85 90 95  
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln  
 100 105 110  
 Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp  
 115 120 125  
 Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu  
 130 135 140  
 His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe  
 145 150 155 160  
 Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr  
 165 170 175  
 Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu  
 180 185 190  
 Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met  
 195 200 205  
 Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu  
 210 215 220  
 Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met  
 225 230 235 240  
 Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe  
 245 250 255  
 Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn  
 260 265 270  
 Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys  
 275 280 285  
 Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Met

292

|   |     |         |
|---|-----|---------|
| 290   | 295 | 300     |
| Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala Arg |     |         |
| 305   | 310 | 315 320 |
| Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp Ser |     |         |
|   | 325 | 330 335 |
| Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly Arg |     |         |
|   | 340 | 345 350 |
| His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu Glu |     |         |
|   | 355 | 360 365 |
| Leu Ala Arg Glu Leu Gly Val Gly Val Ser Ile Trp Glu Leu Ala Arg |     |         |
|   | 370 | 375 380 |
| Ala Trp Thr Thr Ser Thr Thr Cys Ser Arg Trp Ala Leu Arg Pro Pro |     |         |
| 385   | 390 | 395 400 |
| Arg Trp Thr Cys Ser Phe Leu Ser His Gly Val Ser Glu Gln Val Xaa |     |         |
|   | 405 | 410 415 |

&lt;210&gt; 462

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 462

|   |    |       |
|---|----|-------|
| Met Ala Pro Gly Pro Leu Ser Ala Thr Gln Ala Val Val Ile His Thr |    |       |
| 1   | 5  | 10 15 |
| Thr His Cys Leu Gln Leu Pro Val Trp Cys Leu Ser Leu Val Ser Glu |    |       |
|   | 20 | 25 30 |
| Leu Leu Gly Arg Ala Pro Pro His Asn Lys Asp Ala Leu Arg Pro Ser |    |       |
|   | 35 | 40 45 |
| Lys Lys Lys Lys Lys Lys Leu Xaa Gly Gly Pro Val Pro Ile Pro Pro |    |       |
| 50  | 55 | 60    |

&lt;210&gt; 463

&lt;211&gt; 206

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

293

<220>  
 <221> SITE  
 <222> (80)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (93)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (206)  
 <223> Xaa equals stop translation  
  
 <400> 463  
 Met Leu Gly Ala Lys Pro His Trp Leu Pro Gly Pro Leu His Ser Pro  
   1                  5                  10                  15  
 Gly Leu Pro Leu Val Leu Val Leu Leu Ala Leu Gly Ala Gly Trp Ala  
                   20                  25                  30  
 Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val  
           35                  40                  45  
 Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu  
   50                  55                  60  
 Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Ala Ala Val Arg Ser Xaa  
   65                  70                  75                  80  
 His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Xaa Gly Ala Ile  
                   85                  90                  95  
 Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala  
           100                  105                  110  
 Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe  
   115                  120                  125  
 His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met  
   130                  135                  140  
 Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val  
   145                  150                  155                  160  
 Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly  
           165                  170                  175  
 Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Asn Leu Leu Gly Gly Trp  
   180                  185                  190  
 Lys Tyr Ser Ser Phe Ser Gly Phe Leu Ile Phe Pro Leu Xaa  
   195                  200                  205

&lt;210&gt; 464

294

<211> 38  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals stop translation

<400> 464  
 Met Gln Arg Lys Val Ser Asp Phe Ile Ile His Gln Arg Leu Thr Val  
     1                    5                    10                    15  
 Asn Leu Cys Val Ile Ser Phe Phe Phe Phe Leu Pro Ile Cys Ile Phe  
                     20                    25                    30  
 Ser Leu Ala Lys Lys Xaa  
                     35

<210> 465  
 <211> 136  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (136)  
 <223> Xaa equals stop translation

<400> 465  
 Val Val Gly Thr Gly Thr Ser Leu Ala Leu Ser Ser Leu Leu Ser Leu  
     1                    5                    10                    15  
 Leu Leu Phe Ala Gly Met Gln Met Tyr Ser Arg Gln Leu Ala Ser Thr  
                     20                    25                    30  
 Glu Trp Leu Thr Ile Gln Gly Gly Leu Leu Gly Ser Gly Leu Phe Val  
                     35                    40                    45  
 Phe Ser Leu Thr Ala Phe Asn Asn Leu Glu Asn Leu Val Phe Gly Lys  
                     50                    55                    60  
 Gly Phe Gln Ala Lys Ile Phe Pro Glu Ile Leu Leu Cys Leu Leu Leu  
     65                    70                    75                    80  
 Ala Leu Phe Ala Ser Gly Leu Ile His Arg Val Cys Val Thr Thr Cys  
                     85                    90                    95  
 Phe Ile Phe Ser Met Val Gly Leu Tyr Tyr Ile Asn Lys Ile Ser Ser  
                     100                    105                    110  
 Thr Leu Tyr Gln Ala Ala Ala Pro Val Leu Thr Pro Ala Lys Val Thr  
                     115                    120                    125  
 Gly Lys Ser Lys Lys Arg Asn Xaa  
     130                    135

295

<210> 466  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (17)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (18)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (50)  
 <223> Xaa equals stop translation

<400> 466  
 Met Cys Leu Ser Arg Trp Lys Ile Phe Tyr Thr Leu Leu Ile Leu Phe  
           1                  5                  10                  15

Xaa Xaa Phe Ser Ile Thr Ser Glu Xaa Glu Thr Phe Tyr Met Ile Ile  
                   20                  25                  30

Ile His His Asn Pro Thr Gln Ile Thr Ala Ser Cys Ser Phe Thr Phe  
                   35                  40                  45

Leu Xaa  
       50

<210> 467  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (49)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (71)

296

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 467

Met Trp Gly Cys Ser Gly Leu Gly His Arg Thr Val Ser Phe Leu Leu  
 1 5 10 15

Leu Leu Pro Cys Ser Phe Pro Arg Pro Cys Xaa Leu Phe Gly Leu Ile  
 20 25 30

Pro Ile Ser Arg Pro Cys Lys Val Glu Ala Pro Arg Leu Ser Val Pro  
 35 40 45

Xaa Leu Ser Cys Ala Ser His Pro Tyr Cys Asn Cys Pro Met Ser Thr  
 50 55 60

Ser Cys Pro Leu Pro Arg Xaa  
 65 70

&lt;210&gt; 468

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (59)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 468

Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn Pro Pro  
 1 5 10 15

Cys Leu Leu Ser Thr Val Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys  
 20 25 30

Leu Ser Gly Glu Glu Ser Tyr Trp Trp Met Gln Phe Thr Ala Ala Val  
 35 40 45

Glu Phe Ile Lys Thr Ile Asp Asp Arg Lys Xaa  
 50 55

&lt;210&gt; 469

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

297

<220>  
 <221> SITE  
 <222> (35)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 469  
 Met Phe Ser Arg Thr Ser Asn Phe Trp Thr Phe Phe Phe Gln Phe Leu  
   1                  5                  10                  15  
 Ile Phe Lys Val Phe Leu Val Leu Lys Asn Xaa Phe Thr Ser Gln Lys  
                   20                  25                  30  
 Ile Xaa Xaa Ile Xaa Xaa Glu Lys Pro Lys Lys Lys Xaa Arg Gly  
           35                  40                  45  
 Gly Arg Ala Pro Ser Pro Gln Gly Gly Pro Xaa  
       50                  55

<210> 470  
 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (18)  
 <223> Xaa equals stop translation

<400> 470  
 Met Gly Leu Leu Ile Phe Met Leu Leu Ile Gly Ile His Ser Gln Cys  
   1                  5                  10                  15  
 Ser Xaa

<210> 471

298

<211> 316  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (103)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (302)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (305)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (316)  
 <223> Xaa equals stop translation

<400> 471  
 Met Ser Thr Lys Lys Leu Cys Ile Val Gly Gly Ile Leu Leu Val Phe  
   1                  5                  10                  15  
 Gln Ile Ile Ala Phe Leu Val Gly Gly Leu Ile Ala Pro Gly Pro Thr  
                   20                  25                  30  
 Thr Ala Val Ser Tyr Met Ser Val Lys Cys Val Asp Ala Arg Lys Asn  
                   35                  40                  45  
 His His Lys Thr Lys Trp Phe Val Pro Trp Gly Pro Asn His Cys Asp  
   50                  55                  60  
 Lys Ile Arg Asp Ile Glu Glu Ala Ile Pro Arg Glu Ile Glu Ala Asn  
   65                  70                  75                  80  
 Asp Ile Val Phe Ser Val His Ile Pro Leu Pro His Met Glu Met Ser  
                   85                  90                  95  
 Pro Trp Phe Gln Phe Met Xaa Phe Ile Leu Gln Leu Asp Ile Ala Phe  
                   100                  105                  110  
 Lys Leu Asn Asn Gln Ile Arg Glu Asn Ala Glu Val Ser Met Asp Val  
                   115                  120                  125  
 Ser Leu Ala Tyr Arg Asp Asp Ala Phe Ala Glu Trp Thr Glu Met Ala  
   130                  135                  140  
 His Glu Arg Val Pro Arg Lys Leu Lys Cys Thr Phe Thr Ser Pro Lys  
   145                  150                  155                  160  
 Thr Pro Glu His Gly Gly Pro Val Thr Met Asn Val Met Ser Phe Leu  
                   165                  170                  175



299

Ser Trp Lys Leu Gly Leu Trp Pro Met Lys Phe Tyr Leu Leu Asn Ile  
                   180                  185                  190

Arg Leu Pro Val Asn Glu Lys Lys Lys Ile Asn Val Gly Ile Gly Glu  
                   195                  200                  205

Ile Lys Asp Ile Arg Leu Val Gly Ile His Gln Asn Gly Gly Phe Thr  
                   210                  215                  220

Lys Val Trp Phe Ala Met Lys Thr Phe Leu Thr Pro Ser Ile Phe Ile  
                   225                  230                  235                  240

Ile Met Val Trp Tyr Trp Arg Arg Ile Thr Met Met Ser Arg Pro Pro  
                   245                  250                  255

Val Leu Leu Glu Lys Val Ile Phe Ala Leu Gly Ile Ser Met Thr Phe  
                   260                  265                  270

Ile Asn Ile Pro Val Glu Trp Phe Ser Ile Gly Phe Asp Trp Thr Trp  
                   275                  280                  285

Met Leu Leu Phe Gly Asp Ile Arg Gln Ala Ser Ser Met Xaa Cys Phe  
                   290                  295                  300

Xaa Pro Ser Gly Ser Ser Ser Val Ala Ser Thr Xaa  
                   305                  310                  315

&lt;210&gt; 472

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (24)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 472

Met Leu Ala Leu Leu Gly Leu Leu Ala Gly Thr Glu His Pro Pro Gly  
           1                  5                  10                  15

Pro Gln Gly Pro Gly Pro Ser Xaa  
                   20

&lt;210&gt; 473

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 473

Met Pro Ser Gly Ala Cys Cys Ser Pro Xaa

300

1

5

10

&lt;210&gt; 474

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (85)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 474

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Val | Met | Ile | Phe | Lys | Lys | Glu | Phe | Ala | Pro | Ser | Asp | Glu | Glu | Leu |
| 1   |     |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ser | Tyr | Arg | Arg | Gly | Glu | Glu | Trp | Asp | Pro | Gln | Lys | Ala | Glu | Glu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Arg | Asn | Xaa | Lys | Glu | Leu | Ala | Gln | Arg | Gln | Xaa | Gly | Gly | Gly | Ser |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ala | Gly | Ala | Cys | Gly | Gly | Glu | Pro | Cys | Gln | Arg | Leu | Gln | Gly | Gln |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Pro | Pro | His | Arg | Gln | Gly | Ser | Ser | Gln | Arg | Arg | Ser | Pro | His |
|     | 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     | 80  |     |

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| Ala | Thr | Gly | Gln | Xaa |
|     |     |     |     | 85  |

&lt;210&gt; 475

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 475

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Leu | Pro | Ala | Leu | Ser | Thr | Val | Leu | Leu | Pro | Thr | Pro | Ser | Leu | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Asn | Pro | Arg | Glu | Gly | Trp | Ala | Xaa |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

301

20

25

<210> 476  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals stop translation

<400> 476  
 Lys Glu Phe Phe Val Phe Leu Phe Val Cys Leu Phe Trp Leu Leu Ser  
           1                  5                  10                  15

Asn Thr Pro Leu Thr Phe Ile Ser Ile Ile Leu Gln Arg Lys Glu Thr  
                   20                  25                  30

Asn Xaa

<210> 477  
 <211> 172  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (151)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (172)  
 <223> Xaa equals stop translation

<400> 477  
 Met Tyr Ser Leu His Ser Trp Val Gly Leu Ile Ala Val Ile Cys Tyr  
           1                  5                  10                  15

Leu Leu Gln Leu Leu Ser Gly Phe Ser Val Phe Leu Leu Pro Trp Ala  
                   20                  25                  30

Pro Leu Ser Leu Arg Ala Phe Leu Met Pro Ile His Val Tyr Ser Gly  
           35                  40                  45

Ile Val Ile Phe Gly Thr Val Ile Ala Thr Ala Leu Met Gly Leu Thr  
           50                  55                  60

Glu Lys Leu Ile Phe Ser Leu Arg Asp Pro Ala Tyr Ser Thr Phe Pro  
           65                  70                  75                  80

Pro Glu Gly Val Phe Val Asn Thr Leu Gly Leu Leu Ile Leu Val Phe  
                   85                  90                  95

302

Gly Ala Leu Ile Phe Trp Ile Val Thr Arg Pro Gln Trp Lys Arg Pro  
                   100                  105                  110  
 Lys Glu Pro Asn Ser Thr Ile Leu His Pro Asn Gly Gly Thr Glu Gln  
                   115                  120                  125  
 Gly Ala Arg Gly Ser Met Pro Ala Tyr Ser Gly Asn Asn Met Asp Lys  
                   130                  135                  140  
 Ser Asp Ser Glu Leu Asn Xaa Glu Val Ala Ala Arg Lys Arg Asn Leu  
                   145                  150                  155                  160  
 Ala Leu Asp Glu Ala Gly Gln Arg Ser Thr Met Xaa  
                   165                  170

&lt;210&gt; 478

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (61)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 478

Met Cys Ile His Val Phe Met Xaa Val Leu Trp Val Leu Phe Leu Leu  
           1                  5                  10                  15

Asn Pro Leu Cys Thr Gly Leu Trp Pro Leu Xaa Asn Cys Phe Ser Val  
                   20                  25                  30

Leu Arg His Ala Asp Trp Val Leu Gly Ala Asp Tyr Lys Gly Glu Glu  
           35                  40                  45

Leu Asn Arg His Gln Gly Pro Met Lys Pro Lys Asp Xaa  
           50                  55                  60

&lt;210&gt; 479

&lt;211&gt; 3

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

303

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 479

Gly Arg Xaa

1

&lt;210&gt; 480

&lt;211&gt; 96

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (96)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 480

Met Phe His Val Leu Met Ala Gln Val Thr Xaa Val Ile Ile Thr Thr  
1 5 10 15Val Ser Val Leu Val Phe Asp Phe Arg Pro Ser Leu Glu Phe Phe Leu  
20 25 30Glu Ala Xaa Ser Val Xaa Leu Ser Ile Phe Ile Tyr Asn Ala Ser Lys  
35 40 45Pro Gln Val Pro Glu Tyr Ala Pro Arg Gln Glu Arg Ile Arg Asp Leu  
50 55 60Ser Gly Asn Leu Trp Glu Arg Ser Ser Gly Asp Gly Glu Glu Leu Glu  
65 70 75 80Arg Leu Thr Lys Pro Lys Ser Asp Glu Ser Asp Glu Asp Thr Phe Xaa  
85 90 95

&lt;210&gt; 481

&lt;211&gt; 171

&lt;212&gt; PRT

304

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (159)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (171)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 481

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Gly | Pro | Ala | Gln | Ala | Lys | Leu | Leu | Pro | Gly | Ser | Ala | Ile | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Leu | Val | Gly | Leu | Ala | Arg | Pro | Leu | Val | Leu | Ala | Leu | Leu | Leu | Val |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ala | Ala | Leu | Ser | Ser | Val | Val | Ser | Arg | Thr | Asp | Ser | Pro | Ser | Pro |
|     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Leu | Asn | Ser | His | Ile | Ser | Thr | Pro | Asn | Val | Asn | Ala | Leu | Thr |
|     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Glu | Asn | Gln | Thr | Lys | Pro | Ser | Ile | Ser | Gln | Ile | Ser | Thr | Thr | Leu |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Thr | Thr | Ser | Thr | Lys | Lys | Ser | Gly | Gly | Ala | Ser | Val | Val | Pro |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Pro | Ser | Pro | Thr | Pro | Leu | Ser | Gln | Glu | Glu | Ala | Asp | Asn | Asn | Glu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Pro | Ser | Ile | Glu | Glu | Glu | Asp | Leu | Leu | Met | Leu | Asn | Ser | Ser | Pro |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Thr | Ala | Lys | Asp | Thr | Leu | Asp | Asn | Gly | Asp | Tyr | Gly | Glu | Pro | Asp |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Trp | Thr | Thr | Gly | Pro | Arg | Asp | Asp | Asp | Glu | Ser | Asp | Xaa | His |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gly | Arg | Lys | Gln | Gly | Leu | His | Gly | Asn | Xaa |
|     |     |     | 165 |     |     |     |     |     | 170 |     |

&lt;210&gt; 482

&lt;211&gt; 623

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (111)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

305

&lt;221&gt; SITE

&lt;222&gt; (575)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 482

Met Phe Met Arg Ile Ala Lys Ala Tyr Ala Ala Leu Thr Asp Glu Glu  
 1 5 10 15

Ser Arg Lys Asn Trp Glu Glu Phe Gly Asn Pro Asp Gly Pro Gln Ala  
 20 25 30

Thr Ser Phe Gly Ile Ala Leu Pro Ala Trp Ile Val Asp Gln Lys Asn  
 35 40 45

Ser Ile Leu Val Leu Leu Val Tyr Gly Leu Ala Phe Met Val Ile Leu  
 50 55 60

Pro Val Val Val Gly Ser Trp Trp Tyr Arg Ser Ile Arg Tyr Ser Gly  
 65 70 75 80

Asp Gln Ile Leu Ile Arg Thr Thr Gln Ile Tyr Thr Tyr Phe Val Tyr  
 85 90 95

Lys Thr Arg Asn Met Asp Met Lys Arg Leu Ile Met Val Leu Xaa Gly  
 100 105 110

Ala Ser Glu Phe Asp Pro Gln Tyr Asn Lys Asp Ala Thr Ser Arg Pro  
 115 120 125

Thr Asp Asn Ile Leu Ile Pro Gln Leu Ile Arg Glu Ile Gly Ser Ile  
 130 135 140

Asn Leu Lys Lys Asn Glu Pro Pro Leu Thr Cys Pro Tyr Ser Leu Lys  
 145 150 155 160

Ala Arg Val Leu Leu Leu Ser His Leu Ala Arg Met Lys Ile Pro Glu  
 165 170 175

Thr Leu Glu Glu Asp Gln Gln Phe Met Leu Lys Lys Cys Pro Ala Leu  
 180 185 190

Leu Gln Glu Met Val Asn Val Ile Cys Gln Leu Ile Val Met Ala Arg  
 195 200 205

Asn Arg Glu Glu Arg Glu Phe Arg Ala Pro Thr Leu Ala Ser Leu Glu  
 210 215 220

Asn Cys Met Lys Leu Ser Gln Met Ala Val Gln Gly Leu Gln Gln Phe  
 225 230 235 240

Lys Ser Pro Leu Leu Gln Leu Pro His Ile Glu Glu Asp Asn Leu Arg  
 245 250 255

Arg Val Ser Asn His Lys Lys Tyr Lys Ile Lys Thr Ile Gln Asp Leu  
 260 265 270

Val Ser Leu Lys Glu Ser Asp Arg His Thr Leu Leu His Phe Leu Glu  
 275 280 285

306

Asp Glu Lys Tyr Glu Glu Val Met Ala Val Leu Gly Ser Phe Pro Tyr  
 290 295 300  
 Val Thr Met Asp Ile Lys Ser Gln Val Leu Asp Asp Glu Asp Ser Asn  
 305 310 315 320  
 Asn Ile Thr Val Gly Ser Leu Val Thr Val Leu Val Lys Leu Thr Arg  
 325 330 335  
 Gln Thr Met Ala Glu Val Phe Glu Lys Glu Gln Ser Ile Cys Ala Ala  
 340 345 350  
 Glu Glu Gln Pro Ala Glu Asp Gly Gln Gly Glu Thr Asn Lys Asn Arg  
 355 360 365  
 Thr Lys Gly Gly Trp Gln Gln Lys Ser Lys Gly Pro Lys Lys Thr Ala  
 370 375 380  
 Lys Ser Lys Lys Lys Lys Pro Leu Lys Lys Lys Pro Thr Pro Val Leu  
 385 390 395 400  
 Leu Pro Gln Ser Lys Gln Gln Lys Gln Lys Gln Ala Asn Gly Val Val  
 405 410 415  
 Gly Asn Glu Ala Ala Val Lys Glu Asp Glu Glu Glu Val Ser Asp Lys  
 420 425 430  
 Gly Ser Asp Ser Glu Glu Glu Glu Thr Asn Arg Asp Ser Gln Ser Glu  
 435 440 445  
 Lys Asp Asp Gly Ser Asp Arg Asp Ser Asp Arg Glu Gln Asp Glu Lys  
 450 455 460  
 Gln Asn Lys Asp Asp Glu Ala Glu Trp Gln Glu Leu Gln Gln Ser Ile  
 465 470 475 480  
 Gln Arg Lys Glu Arg Ala Leu Leu Glu Thr Lys Ser Lys Ile Thr His  
 485 490 495  
 Pro Val Tyr Ser Leu Tyr Phe Pro Glu Glu Lys Gln Glu Trp Trp Trp  
 500 505 510  
 Leu Tyr Ile Ala Asp Arg Lys Glu Gln Thr Leu Ile Ser Met Pro Tyr  
 515 520 525  
 His Val Cys Thr Leu Lys Asp Thr Glu Glu Val Glu Leu Lys Phe Pro  
 530 535 540  
 Ala Pro Gly Lys Pro Gly Asn Tyr Gln Tyr Thr Val Phe Leu Arg Ser  
 545 550 555 560  
 Asp Ser Tyr Met Gly Leu Asp Gln Ile Lys Pro Leu Glu Val Xaa Lys  
 565 570 575  
 Phe Met Arg Leu Lys Pro Val Pro Glu Asn His Pro Gln Trp Asp Thr  
 580 585 590



307

Ala Ile Glu Gly Asp Glu Asp Gln Glu Asp Ser Glu Gly Phe Glu Asp  
           595                                  600                                  605

Ser Phe Glu Gly Gly Arg Gly Arg Glu Glu Gly Arg Trp Trp Thr  
       610                                  615                                  620

<210> 483  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (92)  
 <223> Xaa equals stop translation

<400> 483  
 Met Lys Ala Ser Gln Cys Cys Cys Cys Leu Ser His Leu Leu Ala Ser  
       1                                  5                                  10                                  15  
 Val Leu Leu Leu Leu Leu Leu Pro Glu Leu Ser Gly Xaa Leu Xaa Val  
                                   20                                  25                                  30  
 Leu Leu Gln Ala Ala Glu Ala Ala Pro Gly Xaa Gly Pro Pro Asp Pro  
           35                                  40                                  45  
 Arg Pro Gly His Tyr Arg Arg Cys His Arg Ala Leu Thr Pro Ala Gln  
       50                                  55                                  60  
 Gln Pro Gly Arg Gly Leu Ala Glu Ala Ala Gly Ala Ala Gly Leu Arg  
       65                                  70                                  75                                  80  
 Gly Arg Gln Trp Gln Gln Pro Cys Gly Arg Ala Xaa  
                                   85                                  90

<210> 484  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<220>

308

<221> SITE  
 <222> (13)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (14)  
 <223> Xaa equals stop translation  
  
 <400> 484  
 Met Phe Lys Cys Leu Gln Thr Thr Phe Leu Phe Ile Xaa Xaa  
   1                  5                  10  
  
 <210> 485  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (54)  
 <223> Xaa equals stop translation  
  
 <400> 485  
 Ile Leu Leu Cys Ser Trp Pro Thr Gly Leu Val Gly Gly Arg Asp Pro  
   1                  5                  10                  15  
  
 Gly Ser Ser Arg Gly Ser Ser Ala Ser Leu Thr Pro Ser Pro Gly Arg  
                   20                  25                  30  
  
 Gln Pro Cys Ser Arg Arg Arg Gly Tyr Ser Val Gly Arg Arg Ser Ser  
           35                  40                  45  
  
 Pro Pro Asp Gly Ser Xaa  
           50  
  
 <210> 486  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (11)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids

309

<220>  
<221> SITE  
<222> (22)  
<223> Xaa equals stop translation

<400> 486  
Met Ala Phe Val Leu Leu Xaa Cys Phe Val Xaa Leu Gln Ser Ser Xaa  
1 5 10 15  
Gly Arg Ala Val Gln Xaa  
20

<210> 487  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 487  
Glu Asn Met Ile Cys Val Lys Cys Leu Pro Gln Tyr Pro Glu His Ser  
1 5 10 15  
Lys His Val

<210> 488  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 488  
Ala Arg Val Ala Phe His Leu Ile Cys Arg Tyr Ile Leu Pro Thr Val  
1 5 10 15  
Tyr Cys His Val  
20

<210> 489  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 489  
Glu Leu Val Glu Ser Pro Gly Ala Ala Gly Asn Ser Ala Arg Ser Gly  
1 5 10 15  
Asn Val Val Cys  
20

<210> 490  
<211> 25  
<212> PRT  
<213> Homo sapiens

<220>

310

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 490

Phe Lys Lys Leu Val Asn Pro Arg Xaa Gln Gly Ile Arg His Glu Glu  
 1 5 10 15

Glu Ala Val Ser Trp Gln Glu Arg Arg  
 20 25

&lt;210&gt; 491

&lt;211&gt; 206

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 491

Ile Ser Val Leu Xaa Tyr Pro His Cys Val Val His Glu Leu Pro Glu  
 1 5 10 15

Leu Thr Ala Glu Ser Leu Glu Ala Gly Asp Ser Asn Gln Phe Cys Trp  
 20 25 30

Arg Asn Leu Phe Ser Cys Ile Asn Leu Leu Arg Ile Leu Asn Lys Leu  
 35 40 45

Thr Lys Trp Lys His Ser Arg Thr Met Met Leu Val Val Phe Lys Ser  
 50 55 60

Ala Pro Ile Leu Lys Arg Ala Leu Lys Val Lys Gln Ala Met Met Gln  
 65 70 75 80

Leu Tyr Val Leu Lys Leu Leu Lys Val Gln Thr Lys Tyr Leu Gly Arg  
 85 90 95

Gln Trp Arg Lys Ser Asn Met Lys Thr Met Ser Ala Ile Tyr Gln Lys  
 100 105 110

Val Arg His Arg Leu Asn Asp Asp Trp Ala Tyr Gly Asn Asp Leu Asp  
 115 120 125

Ala Arg Pro Trp Asp Phe Gln Ala Glu Glu Cys Ala Leu Arg Ala Asn  
 130 135 140

Ile Glu Arg Phe Asn Ala Arg Arg Tyr Asp Arg Ala His Ser Asn Pro  
 145 150 155 160

Asp Phe Leu Pro Val Asp Asn Cys Leu Gln Ser Val Leu Gly Gln Arg  
 165 170 175

Val Asp Leu Pro Glu Asp Phe Gln Met Asn Tyr Asp Leu Trp Leu Glu  
 180 185 190

311

Arg Glu Val Phe Ser Lys Pro Ile Ser Trp Glu Glu Leu Leu  
 195 200 205

&lt;210&gt; 492

&lt;211&gt; 507

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (95)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 492

Met Arg Ala Ala Ser Pro Pro Ala Ser Ala Ser Asp Leu Ile Glu Gln  
 1 5 10 15

Gln Gln Lys Arg Gly Arg Arg Glu His Lys Ala Leu Ile Lys Gln Asp  
 20 25 30

Asn Leu Asp Ala Phe Asn Glu Arg Asp Pro Tyr Lys Ala Asp Asp Ser  
 35 40 45

Arg Glu Glu Glu Glu Glu Asn Asp Asp Asp Asn Ser Leu Glu Gly Glu  
 50 55 60

Thr Phe Pro Leu Glu Arg Asp Glu Val Met Pro Pro Pro Leu Gln His  
 65 70 75 80

Pro Gln Thr Asp Arg Leu Xaa Cys Pro Lys Gly Leu Pro Trp Xaa Pro  
 85 90 95

Lys Val Arg Glu Lys Asp Ile Glu Met Phe Leu Glu Ser Ser Arg Ser  
 100 105 110

Lys Phe Ile Gly Tyr Thr Leu Gly Ser Asp Thr Asn Thr Val Val Gly  
 115 120 125

Leu Pro Arg Pro Ile His Glu Ser Ile Lys Thr Leu Lys Gln His Lys  
 130 135 140

Tyr Thr Ser Ile Ala Glu Val Gln Ala Gln Met Glu Glu Glu Tyr Leu  
 145 150 155 160

Arg Ser Pro Leu Ser Gly Gly Glu Glu Glu Val Glu Gln Val Pro Ala  
 165 170 175

Glu Thr Leu Tyr Gln Gly Leu Leu Pro Ser Leu Pro Gln Tyr Met Ile  
 180 185 190

Ala Leu Leu Lys Ile Leu Leu Ala Ala Ala Pro Thr Ser Lys Ala Lys

312

| 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Asp | Ser | Ile | Asn | Ile | Leu | Ala | Asp | Val | Leu | Pro | Glu | Glu | Met | Pro |
| 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Thr | Thr | Val | Leu | Gln | Ser | Met | Lys | Leu | Gly | Val | Asp | Val | Asn | Arg | His |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Lys | Glu | Val | Ile | Val | Lys | Ala | Ile | Ser | Ala | Val | Leu | Leu | Leu | Leu | Leu |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Lys | His | Phe | Lys | Leu | Asn | His | Val | Tyr | Gln | Phe | Glu | Tyr | Met | Ala | Gln |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| His | Leu | Val | Phe | Ala | Asn | Cys | Ile | Pro | Leu | Ile | Leu | Lys | Phe | Phe | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Gln | Asn | Ile | Met | Ser | Tyr | Ile | Thr | Ala | Lys | Asn | Ser | Ile | Ser | Val | Leu |
| 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |     |
| Asp | Tyr | Pro | His | Cys | Val | Val | His | Glu | Leu | Pro | Glu | Leu | Thr | Ala | Glu |
| 305 |     |     |     | 310 |     |     |     |     |     | 315 |     |     |     |     | 320 |
| Ser | Leu | Glu | Ala | Gly | Asp | Ser | Asn | Gln | Phe | Cys | Trp | Arg | Asn | Leu | Phe |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Cys | Ile | Asn | Leu | Leu | Arg | Ile | Leu | Asn | Lys | Leu | Thr | Lys | Trp | Lys |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| His | Ser | Arg | Thr | Met | Met | Leu | Val | Val | Phe | Lys | Ser | Ala | Pro | Ile | Leu |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Lys | Arg | Ala | Leu | Lys | Val | Lys | Gln | Ala | Met | Met | Gln | Leu | Tyr | Val | Leu |
| 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |     |
| Lys | Leu | Leu | Lys | Val | Gln | Thr | Lys | Tyr | Leu | Gly | Arg | Gln | Trp | Arg | Lys |
| 385 |     |     |     | 390 |     |     |     |     |     | 395 |     |     |     |     | 400 |
| Ser | Asn | Met | Lys | Thr | Met | Ser | Ala | Ile | Tyr | Gln | Lys | Val | Arg | His | Arg |
|     |     |     | 405 |     |     |     |     | 410 |     |     |     |     |     | 415 |     |
| Leu | Asn | Asp | Asp | Trp | Ala | Tyr | Gly | Asn | Asp | Leu | Asp | Ala | Arg | Pro | Trp |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Asp | Phe | Gln | Ala | Glu | Glu | Cys | Ala | Leu | Arg | Ala | Asn | Ile | Glu | Arg | Phe |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Asn | Ala | Arg | Arg | Tyr | Asp | Arg | Ala | His | Ser | Asn | Pro | Asp | Phe | Leu | Pro |
| 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |     |
| Val | Asp | Asn | Cys | Leu | Gln | Ser | Val | Leu | Gly | Gln | Arg | Val | Asp | Leu | Pro |
| 465 |     |     |     | 470 |     |     |     |     |     | 475 |     |     |     | 480 |     |
| Glu | Asp | Phe | Gln | Met | Asn | Tyr | Asp | Leu | Trp | Leu | Glu | Arg | Glu | Val | Phe |
|     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     | 495 |     |
| Ser | Lys | Pro | Ile | Ser | Trp | Glu | Glu | Leu | Leu | Gln |     |     |     |     |     |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     |     |     |     |

313

<210> 493  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 493  
 Met Arg Ala Ala Ser Pro Pro Ala Ser Ala Ser Asp Leu Ile Glu Gln  
 1 5 10 15  
 Gln Gln Lys Arg Gly Arg Arg Glu His Lys Ala Leu Ile Lys Gln Asp  
 20 25 30  
 Asn Leu Asp Ala Phe Asn Glu Arg Asp Pro Tyr Lys Ala Asp Asp Ser  
 35 40 45  
 Arg Glu  
 50

<210> 494  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 494  
 Glu Glu Glu Glu Asn Asp Asp Asp Asn Ser Leu Glu Gly Glu Thr Phe  
 1 5 10 15  
 Pro Leu Glu Arg Asp Glu Val Met Pro Pro Pro Leu Gln His Pro Gln  
 20 25 30  
 Thr Asp Arg Leu Xaa Cys Pro Lys Gly Leu Pro Trp Xaa  
 35 40 45

<210> 495  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 495  
 Pro Lys Val Arg Glu Lys Asp Ile Glu Met Phe Leu Glu Ser Ser Arg  
 1 5 10 15  
 Ser Lys Phe Ile Gly Tyr Thr Leu Gly Ser Asp Thr Asn Thr Val Val  
 20 25 30

314

Gly Leu Pro Arg Pro Ile His Glu Ser Ile Lys Thr Leu Lys Gln His  
35 40 45

Lys Tyr Thr  
50

```
<210> 496
<211> 47
<212> PRT
<213> Homo sapiens
```

<400> 496  
Ser Ile Ala Glu Val Gln Ala Gln Met Glu Glu Glu Tyr Leu Arg Ser  
1 5 10 15

Pro Leu Ser Gly Gly Glu Glu Glu Val Glu Gln Val Pro Ala Glu Thr  
20 25 30

Leu Tyr Gln Gly Leu Leu Pro Ser Leu Pro Gln Tyr Met Ile Ala  
35 40 45

```
<210> 497
<211> 48
<212> PRT
<213> Homo sapiens
```

<400> 497  
Leu Leu Lys Ile Leu Leu Ala Ala Ala Pro Thr Ser Lys Ala Lys Thr  
1 5 10 15

Asp Ser Ile Asn Ile Leu Ala Asp Val Leu Pro Glu Glu Met Pro Thr  
20 25 30

Thr Val Leu Gln Ser Met Lys Leu Gly Val Asp Val Asn Arg His Lys  
35 40 45

```
<210> 498
<211> 50
<212> PRT
<213> Homo sapiens
```

<400> 498  
Glu Val Ile Val Lys Ala Ile Ser Ala Val Leu Leu Leu Leu Lys  
1 5 10 15

His Phe Lys Leu Asn His Val Tyr Gln Phe Glu Tyr Met Ala Gln His  
20 25 30

Leu Val Phe Ala Asn Cys Ile Pro Leu Ile Leu Lys Phe Phe Asn Gln  
35 40 45



315

Asn Ile  
50

<210> 499  
<211> 48  
<212> PRT  
<213> Homo sapiens

<400> 499  
Met Ser Tyr Ile Thr Ala Lys Asn Ser Ile Ser Val Leu Asp Tyr Pro  
1 5 10 15  
His Cys Val Val His Glu Leu Pro Glu Leu Thr Ala Glu Ser Leu Glu  
20 25 30  
Ala Gly Asp Ser Asn Gln Phe Cys Trp Arg Asn Leu Phe Ser Cys Ile  
35 40 45

<210> 500  
<211> 47  
<212> PRT  
<213> Homo sapiens

<400> 500  
Asn Leu Leu Arg Ile Leu Asn Lys Leu Thr Lys Trp Lys His Ser Arg  
1 5 10 15  
Thr Met Met Leu Val Val Phe Lys Ser Ala Pro Ile Leu Lys Arg Ala  
20 25 30  
Leu Lys Val Lys Gln Ala Met Met Gln Leu Tyr Val Leu Lys Leu  
35 40 45

<210> 501  
<211> 45  
<212> PRT  
<213> Homo sapiens

<400> 501  
Leu Lys Val Gln Thr Lys Tyr Leu Gly Arg Gln Trp Arg Lys Ser Asn  
1 5 10 15  
Met Lys Thr Met Ser Ala Ile Tyr Gln Lys Val Arg His Arg Leu Asn  
20 25 30  
Asp Asp Trp Ala Tyr Gly Asn Asp Leu Asp Ala Arg Pro  
35 40 45

<210> 502  
<211> 48  
<212> PRT

316

&lt;213&gt; Homo sapiens

&lt;400&gt; 502

Trp Asp Phe Gln Ala Glu Glu Cys Ala Leu Arg Ala Asn Ile Glu Arg  
1 5 10 15

Phe Asn Ala Arg Arg Tyr Asp Arg Ala His Ser Asn Pro Asp Phe Leu  
20 25 30

Pro Val Asp Asn Cys Leu Gln Ser Val Leu Gly Gln Arg Val Asp Leu  
35 40 45

&lt;210&gt; 503

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 503

Pro Glu Asp Phe Gln Met Asn Tyr Asp Leu Trp Leu Glu Arg Glu Val  
1 5 10 15

Phe Ser Lys Pro Ile Ser Trp Glu Glu Leu Leu Gln  
20 25

&lt;210&gt; 504

&lt;211&gt; 317

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (39)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (40)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (112)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 504

Met Ala Pro Pro Ala Pro Gly Pro Ala Ser Gly Gly Ser Gly Glu Val  
1 5 10 15

Asp Glu Leu Phe Asp Val Lys Asn Ala Phe Tyr Ile Gly Ser Tyr Gln  
20 25 30

Gln Cys Ile Asn Glu Ala Xaa Xaa Val Lys Leu Ser Ser Pro Glu Arg  
35 40 45

317

Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln Arg  
 50 55 60  
 Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro Glu  
 65 70 75 80  
 Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu Ser Arg  
 85 90 95  
 Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg Ser Xaa  
 100 105 110  
 Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile Tyr Leu  
 115 120 125  
 His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly Asp  
 130 135 140  
 Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys Leu Asp  
 145 150 155 160  
 Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp Leu Asp  
 165 170 175  
 Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val Ser Leu Ala  
 180 185 190  
 Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe Gln Glu Met  
 195 200 205  
 Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly Gln Ala Ala  
 210 215 220  
 Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu Gly Leu Leu Gln  
 225 230 235 240  
 Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr Leu Val Asn Leu  
 245 250 255  
 Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu Val Thr Asn Arg  
 260 265 270  
 Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser His Pro Phe Ile Lys  
 275 280 285  
 Glu Tyr Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val Leu Gln Tyr  
 290 295 300  
 Ala Pro Ser Ala Glu Ala Gly Pro Glu Leu Ser Gly Pro  
 305 310 315

&lt;210&gt; 505

&lt;211&gt; 261

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

318

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 505

Arg Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln  
 1 5 10 15

Arg Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro  
 20 25 30

Glu Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu Ser  
 35 40 45

Arg Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg Ser  
 50 55 60

Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile Tyr  
 65 70 75 80

Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly  
 85 90 95

Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys Leu  
 100 105 110

Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp Leu  
 115 120 125

Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val Ser Leu  
 130 135 140

Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe Gln Glu  
 145 150 155 160

Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly Gln Ala  
 165 170 175

Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu Gly Leu Leu  
 180 185 190

Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr Leu Val Asn  
 195 200 205

Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu Val Thr Asn  
 210 215 220

Arg Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser His Pro Phe Ile  
 225 230 235 240

Lys Glu Tyr Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val Leu Gln  
 245 250 255

Tyr Ala Pro Ser Ala  
 260

319

<210> 506  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (39)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (40)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 506  
 Met Ala Pro Pro Ala Pro Gly Pro Ala Ser Gly Gly Ser Gly Glu Val  
           1                  5                  10                  15  
 Asp Glu Leu Phe Asp Val Lys Asn Ala Phe Tyr Ile Gly Ser Tyr Gln  
                   20                  25                  30  
 Gln Cys Ile Asn Glu Ala Xaa Xaa Val Lys Leu Ser Ser Pro Glu Arg  
           35                  40                  45

<210> 507  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 507  
 Asp Val Glu Arg Asp Val Phe Leu Tyr Arg Ala Tyr Leu Ala Gln Arg  
           1                  5                  10                  15  
 Lys Phe Gly Val Val Leu Asp Glu Ile Lys Pro Ser Ser Ala Pro Glu  
                   20                  25                  30  
 Leu Gln Ala Val Arg Met Phe Ala Asp Tyr Leu Ala His Glu Ser  
           35                  40                  45

<210> 508  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (17)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 508  
 Arg Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg Ser  
           1                  5                  10                  15

320

Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile Tyr  
                   20                  25                  30

Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln Gly  
                   35                  40                  45

&lt;210&gt; 509

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 509

Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys Leu  
   1                  5                  10                  15

Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp Leu  
                   20                  25                  30

Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val Ser  
                   35                  40                  45

&lt;210&gt; 510

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 510

Leu Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe Gln  
   1                  5                  10                  15

Glu Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly Gln  
                   20                  25                  30

Ala Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu Gly  
                   35                  40                  45

&lt;210&gt; 511

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 511

Leu Leu Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr Leu  
   1                  5                  10                  15

Val Asn Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu Val  
                   20                  25                  30

Thr Asn Arg Tyr Leu Ser Gln Leu Lys Asp Ala His Arg Ser His Pro  
                   35                  40                  45

```
<210> 512
<211> 32
<212> PRT
<213> Homo sapiens
```

```
<210> 513
<211> 47
<212> PRT
<213> Homo sapiens
```

```
<210> 514
<211> 48
<212> PRT
<213> Homo sapiens
```

```

<400> 514
Ser Arg Arg Asp Ser Ile Val Ala Glu Leu Asp Arg Glu Met Ser Arg
 1          5          10          15

Ser Xaa Asp Val Thr Asn Thr Thr Phe Leu Leu Met Ala Ala Ser Ile
          20          25          30

Tyr Leu His Asp Gln Asn Pro Asp Ala Ala Leu Arg Ala Leu His Gln
 35          40          45

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322

<210> 515  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 515  
 Gly Asp Ser Leu Glu Cys Thr Ala Met Thr Val Gln Ile Leu Leu Lys  
           1                  5                  10                  15  
 Leu Asp Arg Leu Asp Leu Ala Arg Lys Glu Leu Lys Arg Met Gln Asp  
                   20                  25                  30  
 Leu Asp Glu Asp Ala Thr Leu Thr Gln Leu Ala Thr Ala Trp Val  
           35                  40                  45

<210> 516  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 516  
 Ser Leu Ala Thr Gly Gly Glu Lys Leu Gln Asp Ala Tyr Tyr Ile Phe  
           1                  5                  10                  15  
 Gln Glu Met Ala Asp Lys Cys Ser Pro Thr Leu Leu Leu Leu Asn Gly  
                   20                  25                  30  
 Gln Ala Ala Cys His Met Ala Gln Gly Arg Trp Glu Ala Ala Glu  
           35                  40                  45

<210> 517  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 517  
 Gly Leu Leu Gln Glu Ala Leu Asp Lys Asp Ser Gly Tyr Pro Glu Thr  
           1                  5                  10                  15  
 Leu Val Asn Leu Ile Val Leu Ser Gln His Leu Gly Lys Pro Pro Glu  
                   20                  25                  30  
 Val Thr Asn Arg Tyr Leu  
           35

<210> 518  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 518  
 Ser Gln Leu Lys Asp Ala His Arg Ser His Pro Phe Ile Lys Glu Tyr  
           1                  5                  10                  15



323

Gln Ala Lys Glu Asn Asp Phe Asp Arg Leu Val Leu Gln Tyr Ala Pro  
20 25 30

Ser Ala

```
<210> 519
<211> 62
<212> PRT
<213> Homo sapiens
```

```

<400> 519
Asn Arg Tyr Tyr Arg Glu Ser Trp Ser Leu Gln Val Pro Val Arg Asn
  1             5             10             15

```

Ser Gly Ser Thr His Ala Ser Glu Arg Asn Gly Ala Ser Gly Pro Arg  
20 25 30

Pro Gly Leu Arg Arg Leu Arg Gly Gly Arg Arg Ala Val Arg Arg Lys  
35 40 45

Glu Arg Leu Leu His Arg Gln Leu Pro Ala Val His Lys Arg  
50 55 60

```
<210> 520'
<211> 66
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (4)
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 520  
Ala Pro Gly Xaa Gly Trp Arg Gly Ser Leu Gly Glu Pro Pro Pro Pro  
1 5 10 15

Pro Arg Ala Ser Leu Ser Ser Asp Thr Ser Ala Leu Ser Tyr Asp Ser  
20 25 30

Val Lys Tyr Thr Leu Val Val Asp Glu His Ala Gln Leu Glu Leu Val  
35 40 45

Ser Leu Arg Arg Ala Ser Glu Thr Thr Val Thr Arg Val Thr Leu Pro  
50 55 60

Pro Ser  
65

```
<210> 521
<211> 30
<212> PRT
<213> Homo sapiens
```

324

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 521

Ala Pro Gly Xaa Gly Trp Arg Gly Ser Leu Gly Glu Pro Pro Pro Pro  
 1 5 10 15

Pro Arg Ala Ser Leu Ser Ser Asp Thr Ser Ala Leu Ser Tyr  
 20 25 30

&lt;210&gt; 522

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 522

Asp Ser Val Lys Tyr Thr Leu Val Val Asp Glu His Ala Gln Leu Glu  
 1 5 10 15

Leu Val Ser Leu Arg Arg Ala Ser Glu Thr Thr Val Thr Arg Val Thr  
 20 25 30

Leu Pro Pro Ser  
 35

&lt;210&gt; 523

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 523

Met Lys Ala Ile Gly Ile Glu Pro Ser Leu Ala Thr Tyr His His Ile  
 1 5 10 15

Ile Arg Leu Phe Asp Gln Pro Gly Asp Pro Leu Lys Arg Ser Ser Phe  
 20 25 30

Ile Ile Tyr Asp Ile Met Asn Glu Leu Met Gly Lys Arg Phe Ser Pro  
 35 40 45

Lys Asp Pro Asp Asp Asp Lys Phe Phe Gln Ser Ala Met Ser Ile Cys  
 50 55 60

Ser Ser Leu Arg Asp Leu Glu Leu Ala Tyr Gln Val His Gly Leu Leu  
 65 70 75 80

Lys Thr Gly Asp Asn Trp Lys Phe Ile Gly Pro Asp Gln His Arg Asn  
 85 90 95

Phe Tyr Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile  
 100 105 110

Asp Val Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala Tyr Phe

325

115                      120                      125  
 Pro His Ser Gln Thr Met Ile His Leu Leu Gln Ala Leu Asp Val Ala  
       130                      135                      140  
 Asn Arg Leu Glu Val Ile Pro Lys Ile Trp Glu Arg  
 145                      150                      155  
  
 <210> 524  
 <211> 176  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 524  
 Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu Arg Glu  
   1                          5                          10                          15  
 Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu Leu Gln  
                           20                          25                          30  
 Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr Glu Ser  
           35                          40                          45  
 Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser Leu Asn  
   50                          55                          60  
 Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu Ala Trp  
   65                          70                          75                          80  
 Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg Ser Glu  
                           85                          90                          95  
 Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser Pro Ser  
           100                          105                          110  
 Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu Pro Ile  
           115                          120                          125  
 Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile Asn Gln  
   130                          135                          140  
 Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser Asp Ser  
 145                          150                          155                          160  
 Asp Thr Asp Ser Ser Ser Asp Ser Asp Ser Asp Thr Ser Glu Gly Lys  
                           165                          170                          175

<210> 525  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens

<400> 525

326

Met Lys Ala Ile Gly Ile Glu Pro Ser Leu Ala Thr Tyr His His Ile  
 1 5 10 15  
 Ile Arg Leu Phe Asp Gln Pro Gly Asp Pro Leu Lys Arg Ser Ser Phe  
 20 25 30  
 Ile Ile Tyr Asp Ile Met Asn Glu Leu Met Gly Lys Arg Phe Ser Pro  
 35 40 45

Lys

<210> 526  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens

<400> 526  
 Asp Pro Asp Asp Asp Lys Phe Phe Gln Ser Ala Met Ser Ile Cys Ser  
 1 5 10 15  
 Ser Leu Arg Asp Leu Glu Leu Ala Tyr Gln Val His Gly Leu Leu Lys  
 20 25 30  
 Thr Gly Asp Asn Trp Lys Phe Ile Gly Pro Asp Gln His Arg Asn Phe  
 35 40 45

Tyr

<210> 527  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 527  
 Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile Asp Val  
 1 5 10 15  
 Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala  
 20 25

<210> 528  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 528  
 Tyr Phe Pro His Ser Gln Thr Met Ile His Leu Leu Gln Ala Leu Asp  
 1 5 10 15  
 Val Ala Asn Arg Leu Glu Val Ile Pro Lys Ile Trp Glu Arg  
 20 25 30

327

<210> 529  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 529  
 Lys Asp Ser Lys Glu Tyr Gly His Thr Phe Arg Ser Asp Leu Arg Glu  
           1                  5                  10                  15  
 Glu Ile Leu Met Leu Met Ala Arg Asp Lys His Pro Pro Glu Leu Gln  
                   20                  25                  30  
 Val Ala Phe Ala Asp Cys Ala Ala Asp Ile Lys Ser Ala Tyr  
           35                  40                  45

<210> 530  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 530  
 Glu Ser Gln Pro Ile Arg Gln Thr Ala Gln Asp Trp Pro Ala Thr Ser  
           1                  5                  10                  15  
 Leu Asn Cys Ile Ala Ile Leu Phe Leu Arg Ala Gly Arg Thr Gln Glu  
                   20                  25                  30  
 Ala Trp Lys Met Leu Gly Leu Phe Arg Lys His Asn Lys Ile Pro Arg  
           35                  40                  45  
 Ser Glu  
           50

<210> 531  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 531  
 Leu Leu Asn Glu Leu Met Asp Ser Ala Lys Val Ser Asn Ser Pro Ser  
           1                  5                  10                  15  
 Gln Ala Ile Glu Val Val Glu Leu Ala Ser Ala Phe Ser Leu Pro Ile  
                   20                  25                  30  
 Cys Glu Gly Leu Thr Gln Arg Val Met Ser Asp Phe Ala Ile Asn  
           35                  40                  45

<210> 532  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 532  
 Gln Glu Gln Lys Glu Ala Leu Ser Asn Leu Thr Ala Leu Thr Ser Asp

328

|  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |    |
|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|----|
| 1  |     |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     |     |  | 15 |
| Ser  | Asp | Thr | Asp | Ser | Ser | Ser | Asp | Ser | Asp | Ser | Asp | Thr | Ser | Glu | Gly |  |    |
|  |     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |  |    |
| Lys  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |    |
| <p>&lt;210&gt; 533<br/>         &lt;211&gt; 324<br/>         &lt;212&gt; PRT<br/>         &lt;213&gt; Homo sapiens</p> |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |    |
| <p>&lt;400&gt; 533</p>   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |    |
| Met  | Ser | Ser | Asp | Asn | Glu | Ser | Asp | Ile | Glu | Asp | Glu | Asp | Leu | Lys | Leu |  |    |
| 1  |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |    |
| Glu  | Leu | Arg | Arg | Leu | Arg | Asp | Lys | His | Leu | Lys | Glu | Ile | Gln | Asp | Leu |  |    |
|  |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |    |
| Gln  | Ser | Arg | Gln | Lys | His | Glu | Ile | Glu | Ser | Leu | Tyr | Thr | Lys | Leu | Gly |  |    |
|  |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |    |
| Lys  | Val | Pro | Pro | Ala | Val | Ile | Ile | Pro | Pro | Ala | Ala | Pro | Leu | Ser | Gly |  |    |
|  | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |    |
| Arg  | Arg | Arg | Arg | Pro | Thr | Lys | Ser | Lys | Gly | Ser | Lys | Ser | Ser | Arg | Ser |  |    |
| 65   |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |    |
| Ser  | Ser | Leu | Gly | Asn | Lys | Ser | Pro | Gln | Leu | Ser | Gly | Asn | Leu | Ser | Gly |  |    |
|  |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |    |
| Gln  | Ser | Ala | Ala | Ser | Val | Leu | His | Pro | Gln | Gln | Thr | Leu | His | Pro | Pro |  |    |
|  |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |    |
| Gly  | Asn | Ile | Pro | Glu | Ser | Gly | Gln | Asn | Gln | Leu | Leu | Gln | Pro | Leu | Lys |  |    |
|  | 115 |     |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |    |
| Pro  | Ser | Pro | Ser | Ser | Asp | Asn | Leu | Tyr | Ser | Ala | Phe | Thr | Ser | Asp | Gly |  |    |
|  | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |    |
| Ala  | Ile | Ser | Val | Pro | Ser | Leu | Ser | Ala | Pro | Gly | Gln | Gly | Thr | Ser | Ser |  |    |
| 145  |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |    |
| Thr  | Asn | Thr | Val | Gly | Ala | Thr | Val | Asn | Ser | Gln | Ala | Ala | Gln | Ala | Gln |  |    |
|  |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |    |
| Pro  | Pro | Ala | Met | Thr | Ser | Ser | Arg | Lys | Gly | Thr | Phe | Thr | Asp | Asp | Leu |  |    |
|  |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |    |
| His  | Lys | Leu | Val | Asp | Asn | Trp | Ala | Arg | Asp | Ala | Met | Asn | Leu | Ser | Gly |  |    |
|  | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |    |
| Arg  | Arg | Gly | Ser | Lys | Gly | His | Met | Asn | Tyr | Glu | Gly | Pro | Gly | Met | Ala |  |    |
|  | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |    |
| Arg  | Lys | Phe | Ser | Ala | Pro | Gly | Gln | Leu | Cys | Ile | Ser | Met | Thr | Ser | Asn |  |    |

329

225                      230                      235                      240  
 Leu Gly Gly Ser Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly  
                                  245                      250                      255  
 His Phe Thr Lys Ser Met Cys Pro Pro Gln Gln Tyr Gly Phe Pro Ala  
                                  260                      265                      270  
 Thr Pro Phe Gly Ala Gln Trp Ser Gly Thr Gly Gly Pro Ala Pro Gln  
                                  275                      280                      285  
 Pro Leu Gly Gln Phe Gln Pro Val Gly Thr Ala Ser Leu Gln Asn Phe  
                                  290                      295                      300  
 Asn Ile Ser Asn Leu Gln Lys Ser Ile Ser Asn Pro Pro Gly Ser Asn  
 305                      310                      315                      320  
 Leu Arg Thr Thr

<210> 534  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<400> 534  
 Ile Gln Asp Leu Gln Ser Arg Gln Lys His Glu Ile Glu Ser Leu Tyr  
 1                      5                      10                      15  
 Thr Lys Leu Gly Lys Val Pro Pro Ala Val Ile Ile Pro Pro Ala Ala  
                                  20                      25                      30  
 Pro Leu Ser Gly Arg Arg Arg Arg Pro Thr Lys Ser Lys Gly Ser Lys  
                                  35                      40                      45  
 Ser Ser Arg Ser Ser Ser Leu Gly Asn Lys Ser Pro Gln Leu Ser Gly  
                                  50                      55                      60  
 Asn Leu Ser Gly Gln Ser Ala Ala Ser Val Leu His Pro Gln Gln Thr  
 65                      70                      75                      80  
 Leu His Pro Pro Gly Asn Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu  
                                  85                      90                      95  
 Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe  
                                  100                      105                      110  
 Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly Gln  
                                  115                      120                      125  
 Gly Thr Ser Ser Thr  
 130

<210> 535  
 <211> 53  
 <212> PRT

330

&lt;213&gt; Homo sapiens

&lt;400&gt; 535

Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly Gln  
 1 5 10 15

Gly Thr Ser Ser Thr Asn Thr Val Gly Ala Thr Val Asn Ser Gln Ala  
 20 25 30

Ala Gln Ala Gln Pro Pro Ala Met Thr Ser Ser Arg Lys Gly Thr Phe  
 35 40 45

Thr Asp Asp Leu His  
 50

&lt;210&gt; 536

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 536

Lys Gly His Met Asn Tyr Glu Gly Pro Gly Met Ala Arg Lys Phe Ser  
 1 5 10 15

Ala Pro Gly Gln Leu Cys Ile Ser Met Thr Ser Asn Leu Gly Gly Ser  
 20 25 30

Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly His Phe Thr Lys  
 35 40 45

&lt;210&gt; 537

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 537

Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe  
 1 5 10 15

Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro Gly  
 20 25 30

&lt;210&gt; 538

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 538

Met Ser Ser Asp Asn Glu Ser Asp Ile Glu Asp Glu Asp Leu Lys Leu  
 1 5 10 15

Glu Leu Arg Arg Leu Arg Asp Lys His Leu Lys Glu Ile Gln Asp Leu



331

20 25 30

Gln Ser Arg Gln Lys His Glu Ile Glu Ser Leu Tyr Thr Lys Leu Gly  
 35 40 45

Lys Val Pro  
 50

<210> 539  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 539  
 Pro Ala Val Ile Ile Pro Pro Ala Ala Pro Leu Ser Gly Arg Arg Arg  
 1 5 10 15

Arg Pro Thr Lys Ser Lys Gly Ser Lys Ser Ser Arg Ser Ser Ser Leu  
 20 25 30

Gly Asn Lys Ser Pro Gln Leu Ser Gly Asn Leu Ser Gly Gln Ser  
 35 40 45

<210> 540  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 540  
 Ala Ala Ser Val Leu His Pro Gln Gln Thr Leu His Pro Pro Gly Asn  
 1 5 10 15

Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu Gln Pro Leu Lys Pro Ser  
 20 25 30

Pro Ser Ser Asp Asn Leu Tyr Ser Ala Phe Thr Ser Asp Gly Ala Ile  
 35 40 45

Ser Val  
 50

<210> 541  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 541  
 Pro Ser Leu Ser Ala Pro Gly Gln Gly Thr Ser Ser Thr Asn Thr Val  
 1 5 10 15

Gly Ala Thr Val Asn Ser Gln Ala Ala Gln Ala Gln Pro Pro Ala Met  
 20 25 30

Thr Ser Ser Arg Lys Gly Thr Phe Thr Asp Asp Leu  
 35 40

332

<210> 542  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 542  
 His Lys Leu Val Asp Asn Trp Ala Arg Asp Ala Met Asn Leu Ser Gly  
     1                    5                    10                    15  
 Arg Arg Gly Ser Lys Gly His Met Asn Tyr Glu Gly Pro Gly Met Ala  
             20                    25                    30  
 Arg Lys Phe Ser Ala Pro Gly Gln Leu Cys Ile Ser Met Thr  
             35                    40                    45

<210> 543  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 543  
 Ser Asn Leu Gly Gly Ser Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser  
     1                    5                    10                    15  
 Leu Gly His Phe Thr Lys Ser Met Cys Pro Pro Gln Gln Tyr Gly Phe  
             20                    25                    30  
 Pro Ala Thr Pro Phe Gly Ala Gln Trp Ser Gly Thr Gly Gly  
             35                    40                    45

<210> 544  
 <211> 40  
 <212> PRT  
 <213> Homo sapiens

<400> 544  
 Pro Ala Pro Gln Pro Leu Gly Gln Phe Gln Pro Val Gly Thr Ala Ser  
     1                    5                    10                    15  
 Leu Gln Asn Phe Asn Ile Ser Asn Leu Gln Lys Ser Ile Ser Asn Pro  
             20                    25                    30  
 Pro Gly Ser Asn Leu Arg Thr Thr  
             35                    40

<210> 545  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (10)

333

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 545

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Arg | Val | Ala | Ala | Ala | Glu | Ser | Met | Xaa | Leu | Leu | Leu | Glu | Cys | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Val | Arg | Gly | Pro | Glu | Tyr | Leu | Thr | Gln | Met | Trp | His | Phe | Met | Cys |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ala | Leu | Ile | Lys | Ala | Ile | Gly | Thr | Glu | Pro | Asp | Ser | Asp | Val | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Ile | Met | His | Ser | Phe | Ala | Lys |
|     | 50  |     |     |     |     |     | 55  |     |

&lt;210&gt; 546

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 546

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Ile | Asn | Asn | Gln | Asn | Cys | Phe | Ile | Val | Ile | Asp | Leu | Val | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Met | Glu | Asn | Gly | Val | Glu | Gly | Leu | Leu | Ile | Phe | Gly | Ala | Phe |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Glu | Ser | Trp | Leu | Ile | Gly | Val | Arg | Cys | Ser | Ser | Glu | Pro | Pro |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ala | Leu | Leu | Leu | Ile | Leu | Ala | His | Ser | Gln | Lys | Arg | Arg | Leu | Asp |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Trp | Ser | Phe | Ile | Arg | His | Leu | Arg | Val | His | Tyr | Cys | Val | Ser | Leu |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| Thr | Ile | His | Phe | Ser |
|     |     |     |     | 85  |

&lt;210&gt; 547

&lt;211&gt; 100

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

334

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 547

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Arg | Glu | Ala | Asn | Lys | Xaa | Phe | Phe | Ile | Glu | Ser | Cys | Ile | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Val | Ser | Phe | Ile | Ile | Asn | Val | Phe | Val | Val | Ser | Val | Phe | Ala |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Xaa | Phe | Phe | Gly | Xaa | Thr | Asn | Glu | Gln | Val | Val | Glu | Val | Cys | Thr |
|     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Thr | Ser | Ser | Pro | His | Ala | Gly | Leu | Phe | Pro | Lys | Asp | Asn | Ser | Thr |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ala | Val | Asp | Ile | Tyr | Lys | Gly | Gly | Val | Val | Leu | Gly | Cys | Tyr | Phe |
| 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Ala | Ala | Leu | Tyr | Ile | Trp | Ala | Val | Gly | Ile | Leu | Ala | Ala | Gly |
|     |     |     |     | 85  |     |     |     | 90  |     |     |     |     |     | 95  |     |

|     |     |     |     |
|-----|-----|-----|-----|
| Gln | Ser | Ser | Thr |
|     |     |     | 100 |

&lt;210&gt; 548

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 548

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Arg | Glu | Ala | Asn | Lys | Xaa | Phe | Phe | Ile | Glu | Ser | Cys | Ile | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Val | Ser | Phe | Ile | Ile | Asn | Val | Phe | Val | Val | Ser | Val | Phe | Ala |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

335

Glu Xaa Phe Phe Gly Xaa Thr Asn Glu Gln Val Val Glu  
35 40 45

<210> 549  
<211> 55  
<212> PRT  
<213> Homo sapiens

<400> 549  
Val Cys Thr Asn Thr Ser Ser Pro His Ala Gly Leu Phe Pro Lys Asp  
1 5 10 15

Asn Ser Thr Leu Ala Val Asp Ile Tyr Lys Gly Gly Val Val Leu Gly  
20 25 30

Cys Tyr Phe Gly Pro Ala Ala Leu Tyr Ile Trp Ala Val Gly Ile Leu  
35 40 45

Ala Ala Gly Gln Ser Ser Thr  
50 55

<210> 550  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 550  
Gln Asp Lys His Ala Glu Glu Val Arg Lys Asn Lys Glu Leu Lys Glu  
1 5 10 15

Glu Ala Ser Arg  
20

<210> 551  
<211> 92  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (16)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (17)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (20)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE

336

&lt;222&gt; (24)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 551

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gln | Asp | Leu | Ser | Pro | Trp | Ala | Ala | Pro | Val | Gly | Cys | Pro | Leu | Xaa |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Ala | Ser | Xaa | Thr | Cys | His | Xaa | Leu | Pro | Leu | Ser | Gly | Cys | Leu | Arg |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Gln | Ser | Xaa | Ser | Leu | Pro | Val | Val | Ala | Xaa | Leu | Cys | Phe | Trp | Phe |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Cys | Pro | Leu | Ala | Ser | Leu | Phe | Val | Pro | Gly | Gln | Pro | Cys | Val | Thr |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Pro | Phe | Pro | Ser | Leu | Pro | Phe | Gln | Asp | Lys | His | Ala | Glu | Glu | Val |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Lys | Asn | Lys | Glu | Leu | Lys | Glu | Glu | Ala | Ser | Arg |
|     |     |     |     | 85  |     |     |     |     |     | 90  |     |

&lt;210&gt; 552

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 552

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Thr | Arg | Cys | Cys | Thr | Thr | Gln | Pro | Cys | Arg | Ser | Ser | Ala | Arg | Arg |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Cys | Trp | Val | Pro | Met | Val | Pro | Ser | Pro | Glu | Gly | Arg | Glu | Xaa | Gln |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| Pro | Thr | Cys | Pro | Ser |
|     |     |     | 35  |     |

&lt;210&gt; 553

&lt;211&gt; 363

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

337

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (211)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 553

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Arg | Ser | Leu | Asn | Glu | Asn | Ser | Ala | Arg | Ser | Thr | Ala | Gly | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Val | Pro | Leu | Phe | Asn | Gln | Lys | Lys | Arg | Asn | Arg | Gln | Pro | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Asn | Pro | Leu | Lys | Asp | Asp | Ser | Gly | Ile | Ser | Thr | Pro | Ser | Asp |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Tyr | Asp | Phe | Pro | Pro | Leu | Pro | Thr | Asp | Trp | Ala | Trp | Glu | Ala | Val |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Pro | Glu | Xaa | Ala | Pro | Val | Met | Lys | Thr | Val | Asp | Thr | Gly | Gln | Ile |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | His | Ser | Val | Ser | Arg | Pro | Leu | Arg | Ser | Gln | Asp | Ser | Val | Phe | Asn |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ile | Gln | Ser | Asn | Thr | Gly | Arg | Ser | Gln | Gly | Gly | Trp | Ser | Tyr | Arg |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Gly | Asn | Lys | Asn | Thr | Ser | Leu | Lys | Thr | Trp | Xaa | Lys | Asn | Asp | Phe |
|     | 115 |     |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Pro | Gln | Cys | Lys | Arg | Thr | Asn | Leu | Val | Ala | Asn | Asp | Gly | Lys | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Cys | Pro | Met | Ser | Ser | Gly | Ala | Gln | Gln | Gln | Lys | Gln | Leu | Arg | Thr |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Pro | Pro | Asn | Leu | Ser | Arg | Asn | Lys | Glu | Thr | Glu | Leu | Leu | Arg |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Thr | His | Ser | Ser | Lys | Ile | Ser | Gly | Cys | Thr | Met | Arg | Gly | Leu | Asp |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     |     | 190 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asn | Ser | Ala | Leu | Gln | Thr | Leu | Lys | Pro | Asn | Phe | Gln | Gln | Asn | Gln |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Lys | Xaa | Gln | Met | Leu | Asp | Asp | Ile | Pro | Glu | Asp | Asn | Thr | Leu | Lys |
|     | 210 |     |     |     |     | 215 |     |     |     |     |     | 220 |     |     |     |

338

Glu Thr Ser Leu Tyr Gln Leu Gln Phe Lys Glu Lys Ala Ser Ser Leu  
 225 230 235 240  
 Arg Ile Ile Ser Ala Val Ile Glu Ser Met Lys Tyr Trp Arg Glu His  
 245 250 255  
 Ala Gln Lys Thr Val Leu Leu Phe Glu Val Leu Ala Val Leu Asp Ser  
 260 265 270  
 Ala Val Thr Pro Gly Pro Tyr Tyr Ser Lys Thr Phe Leu Met Arg Asp  
 275 280 285  
 Gly Lys Asn Thr Leu Pro Cys Val Phe Tyr Glu Ile Asp Arg Glu Leu  
 290 295 300  
 Pro Arg Leu Ile Arg Gly Arg Val His Arg Cys Val Gly Asn Tyr Asp  
 305 310 315 320  
 Gln Lys Lys Asn Ile Phe Gln Cys Val Ser Val Arg Pro Ala Ser Val  
 325 330 335  
 Ser Glu Gln Lys Thr Phe Gln Ala Phe Val Lys Ile Ala Asp Val Glu  
 340 345 350  
 Met Gln Tyr Tyr Ile Asn Val Met Asn Glu Thr  
 355 360

&lt;210&gt; 554

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 554

Ser Gln Asp Ser Val Phe Asn Ser Ile Gln Ser Asn Thr Gly Arg Ser  
 1 5 10 15

Gln Gly Gly Trp Ser Tyr Arg Asp Gly Asn Lys Asn Thr Ser Leu Lys  
 20 25 30

Thr Trp Xaa Lys Asn Asp Phe Lys Pro Gln Cys Lys Arg  
 35 40 45

&lt;210&gt; 555

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 555

Asn Lys Glu Thr Glu Leu Leu Arg Gln Thr His Ser Ser Lys Ile Ser  
 1 5 10 15



339

Gly Cys Thr Met Arg Gly Leu Asp Lys Asn Ser Ala Leu Gln Thr Leu  
20 25 30

Lys Pro Asn Phe  
35

<210> 556  
<211> 49  
<212> PRT  
<213> Homo sapiens

<400> 556  
Ser Ser Leu Arg Ile Ile Ser Ala Val Ile Glu Ser Met Lys Tyr Trp  
1 5 10 15

Arg Glu His Ala Gln Lys Thr Val Leu Leu Phe Glu Val Leu Ala Val  
20 25 30

Leu Asp Ser Ala Val Thr Pro Gly Pro Tyr Tyr Ser Lys Thr Phe Leu  
35 40 45

Met

<210> 557  
<211> 42  
<212> PRT  
<213> Homo sapiens

<400> 557  
Pro Arg Leu Ile Arg Gly Arg Val His Arg Cys Val Gly Asn Tyr Asp  
1 5 10 15

Gln Lys Lys Asn Ile Phe Gln Cys Val Ser Val Arg Pro Ala Ser Val  
20 25 30

Ser Glu Gln Lys Thr Phe Gln Ala Phe Val  
35 40

<210> 558  
<211> 370  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (320)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (334)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (337)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (339)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (341)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (345)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (350)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (352)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (355)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (360)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 558  
 Gly Val Phe Arg Pro Cys Val Cys Gly Arg Pro Ala Ser Leu Thr Cys  
 1 5 10 15  
 Ser Pro Leu Asp Pro Glu Val Gly Pro Tyr Cys Asp Thr Pro Thr Met  
 20 25 30  
 Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro Val  
 35 40 45  
 His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys Thr  
 50 55 60  
 Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg Gly  
 65 70 75 80  
 Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His Arg  
 85 90 95

341

Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp Val  
 100 105 110  
 Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr Lys  
 115 120 125  
 Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln Leu  
 130 135 140  
 Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp Val  
 145 150 155 160  
 Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu His  
 165 170 175  
 Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe Arg  
 180 185 190  
 Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr Val  
 195 200 205  
 Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu Val  
 210 215 220  
 Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met Leu  
 225 230 235 240  
 Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu Leu  
 245 250 255  
 Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met Phe  
 260 265 270  
 Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe Ser  
 275 280 285  
 Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn Ala  
 290 295 300  
 Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys Xaa  
 305 310 315 320  
 Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr Ser Met Xaa Trp Thr  
 325 330 335  
 Xaa Arg Xaa Pro Xaa Asp Ala Arg Xaa Pro Val Val Gly Xaa Arg Xaa  
 340 345 350  
 Ile Gln Xaa Leu Lys Asp His Xaa Pro Arg Met Val Leu Asp Ser Lys  
 355 360 365  
 Pro Gln  
 370

&lt;210&gt; 559

&lt;211&gt; 39

342

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 559

Thr Cys Ser Pro Leu Asp Pro Glu Val Gly Pro Tyr Cys Asp Thr Pro  
 1 5 10 15

Thr Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser  
 20 25 30

Pro Val His Thr Thr Leu Ser  
 35

&lt;210&gt; 560

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 560

Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His Arg  
 1 5 10 15

Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp Val  
 20 25 30

Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr Lys  
 35 40 45

Val Phe Gly Ser Lys Phe  
 50

&lt;210&gt; 561

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 561

Arg Glu Met Phe Glu Val Thr Gly Leu His Asp Val Asp Gln Gly Trp  
 1 5 10 15

Met Arg Ala Val Arg Lys His Ala Lys Gly Leu His Ile Val Pro Arg  
 20 25 30

Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe Arg Asn Val Leu Asp  
 35 40 45

Ser Glu Asp Glu  
 50

&lt;210&gt; 562

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 562

343

His Phe Asp Gly Phe Val Val Glu Val Trp Asn Gln Leu Leu Ser Gln  
 1 5 10 15  
 Lys Arg Val Gly Leu Ile His Met Leu Thr His Leu Ala Glu Ala Leu  
 20 25 30  
 His Gln Ala Arg Leu Leu Ala Leu Leu Val Ile Pro Pro Ala Ile Thr  
 35 40 45  
 Pro Gly Thr Asp Gln Leu Gly Met  
 50 55

&lt;210&gt; 563

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 563

Asp Gly Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro  
 1 5 10 15  
 Gly Pro Asn Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu  
 20 25 30  
 Asp Pro Lys Xaa Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr  
 35 40 45

&lt;210&gt; 564

&lt;211&gt; 152

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 564

Glu Arg Gly Val Ser Ile Asn Gln Phe Cys Lys Glu Phe Asn Glu Arg  
 1 5 10 15  
 Thr Lys Asp Ile Lys Glu Gly Ile Pro Leu Pro Thr Lys Ile Leu Val  
 20 25 30  
 Lys Pro Asp Arg Thr Phe Glu Ile Lys Ile Gly Gln Pro Thr Val Ser  
 35 40 45  
 Tyr Phe Leu Lys Ala Ala Ala Gly Ile Glu Lys Gly Ala Arg Gln Thr  
 50 55 60  
 Gly Lys Glu Val Ala Gly Leu Val Thr Leu Lys His Val Tyr Glu Ile  
 65 70 75 80  
 Ala Arg Ile Lys Ala Gln Asp Glu Ala Phe Ala Leu Gln Asp Val Pro  
 85 90 95

344

Leu Ser Ser Val Val Arg Ser Ile Ile Gly Ser Ala Arg Ser Leu Gly  
100 105 110  
Ile Arg Val Val Lys Asp Leu Ser Ser Glu Glu Leu Ala Ala Phe Gln  
115 120 125  
Lys Glu Arg Ala Ile Phe Leu Ala Ala Gln Lys Glu Ala Asp Leu Ala  
130 135 140  
Ala Gln Glu Glu Ala Ala Lys Lys  
145 150

<210> 565  
<211> 51  
<212> PRT  
<213> Homo sapiens

<400> 565  
Glu Arg Gly Val Ser Ile Asn Gln Phe Cys Lys Glu Phe Asn Glu Arg  
1 5 10 15  
Thr Lys Asp Ile Lys Glu Gly Ile Pro Leu Pro Thr Lys Ile Leu Val  
20 25 30  
Lys Pro Asp Arg Thr Phe Glu Ile Lys Ile Gly Gln Pro Thr Val Ser  
35 40 45  
Tyr Phe Leu  
50

<210> 566  
<211> 49  
<212> PRT  
<213> Homo sapiens

<400> 566  
Lys Ala Ala Ala Gly Ile Glu Lys Gly Ala Arg Gln Thr Gly Lys Glu  
1 5 10 15  
Val Ala Gly Leu Val Thr Leu Lys His Val Tyr Glu Ile Ala Arg Ile  
20 25 30  
Lys Ala Gln Asp Glu Ala Phe Ala Leu Gln Asp Val Pro Leu Ser Ser  
35 40 45  
Val

<210> 567  
<211> 52  
<212> PRT  
<213> Homo sapiens

<400> 567  
Val Arg Ser Ile Ile Gly Ser Ala Arg Ser Leu Gly Ile Arg Val Val

345

1                      5                      10                      15  
 Lys Asp Leu Ser Ser Glu Glu Leu Ala Ala Phe Gln Lys Glu Arg Ala  
                          20                                      25                                      30  
 Ile Phe Leu Ala Ala Gln Lys Glu Ala Asp Leu Ala Ala Gln Glu Glu  
                          35                                      40                                      45  
 Ala Ala Lys Lys  
                          50  
  
 <210> 568  
 <211> 270  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 568  
 Ala Val Tyr Thr Tyr His Glu Lys Lys Lys Asp Thr Ala Ala Ser Gly  
   1                                      5                                      10                                      15  
 Tyr Gly Thr Gln Asn Ile Arg Leu Ser Arg Asp Ala Val Lys Asp Phe  
                          20                                      25                                      30  
 Asp Cys Cys Cys Leu Ser Leu Gln Pro Cys His Asp Pro Val Val Thr  
                          35                                      40                                      45  
 Pro Asp Gly Tyr Leu Tyr Glu Arg Glu Ala Ile Leu Glu Tyr Ile Leu  
                          50                                      55                                      60  
 His Gln Lys Lys Glu Ile Ala Arg Gln Met Lys Ala Tyr Glu Lys Gln  
   65                                      70                                      75                                      80  
 Arg Gly Thr Arg Arg Glu Glu Gln Lys Glu Leu Gln Arg Ala Ala Ser  
    85                                      90                                      95  
 Gln Asp His Val Arg Gly Phe Leu Glu Lys Glu Ser Ala Ile Val Ser  
    100                                      105                                      110  
 Arg Pro Leu Asn Pro Phe Thr Ala Lys Ala Leu Ser Gly Thr Ser Pro  
    115                                      120                                      125  
 Asp Asp Val Gln Pro Gly Pro Ser Val Gly Pro Pro Ser Lys Asp Lys  
    130                                      135                                      140  
 Asp Lys Val Leu Pro Ser Phe Trp Ile Pro Ser Leu Thr Pro Glu Ala  
   145                                      150                                      155                                      160  
 Lys Ala Thr Lys Leu Glu Lys Pro Ser Arg Thr Val Thr Cys Pro Met  
    165                                      170                                      175  
 Ser Gly Lys Pro Leu Arg Met Ser Asp Leu Thr Pro Val His Phe Thr  
    180                                      185                                      190  
 Pro Leu Asp Ser Ser Val Asp Arg Val Gly Leu Ile Thr Arg Ser Glu  
    195                                      200                                      205  
 Arg Tyr Val Cys Ala Val Thr Arg Asp Ser Leu Ser Asn Ala Thr Pro

346

|   |     |         |
|---|-----|---------|
| 210   | 215 | 220     |
| Cys Ala Val Leu Arg Pro Ser Gly Ala Val Val Thr Leu Glu Cys Val |     |         |
| 225   | 230 | 235 240 |
| Glu Lys Leu Ile Arg Lys Asp Met Val Asp Pro Val Thr Gly Asp Lys |     |         |
|   | 245 | 250 255 |
| Leu Thr Asp Arg Asp Ile Ile Val Leu Gln Arg Gly Gly Thr         |     |         |
|   | 260 | 265 270 |

<210> 569  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<400> 569  
 Tyr Leu Tyr Glu Arg Glu Ala Ile Leu Glu Tyr Ile Leu His Gln Lys  
 1 5 10 15  
 Lys Glu Ile Ala Arg Gln Met Lys Ala Tyr Glu Lys Gln Arg Gly Thr  
 20 25 30  
 Arg Arg Glu Glu Gln Lys Glu Leu Gln Arg Ala Ala Ser Gln Asp His  
 35 40 45  
 Val Arg Gly Phe Leu Glu  
 50

<210> 570  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<400> 570  
 Phe Thr Ala Lys Ala Leu Ser Gly Thr Ser Pro Asp Asp Val Gln Pro  
 1 5 10 15  
 Gly Pro Ser Val Gly Pro Pro Ser Lys Asp Lys Asp Lys Val Leu Pro  
 20 25 30  
 Ser Phe Trp Ile Pro Ser Leu Thr Pro Glu Ala Lys Ala Thr Lys Leu  
 35 40 45  
 Glu Lys Pro Ser Arg Thr Val Thr Cys Pro Met Ser Gly Lys Pro Leu  
 50 55 60

<210> 571  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens



347

&lt;400&gt; 571

Val His Phe Thr Pro Leu Asp Ser Ser Val Asp Arg Val Gly Leu Ile  
 1 5 10 15

Thr Arg Ser Glu Arg Tyr Val Cys Ala Val Thr Arg Asp Ser Leu Ser  
 20 25 30

Asn Ala Thr Pro Cys Ala Val Leu Arg Pro Ser Gly Ala Val Val Thr  
 35 40 45

Leu Glu Cys Val Glu Lys Leu Ile  
 50 55

&lt;210&gt; 572

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

Met Ser Asp Leu Thr Pro Val His Phe Thr Pro Leu Asp Ser Ser Val  
 1 5 10 15

Asp Arg Val Gly Leu Ile Thr Arg Ser Glu Arg Tyr Val Cys Ala Val  
 20 25 30

Thr Arg Asp Ser Leu Ser Asn Ala Thr Pro Cys Ala Val Leu Arg Pro  
 35 40 45

Ser Gly Ala Val Val Thr Leu Glu Cys Val Glu Lys Leu Ile Arg Lys  
 50 55 60

Asp Met  
 65

&lt;210&gt; 573

&lt;211&gt; 567

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (409)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 573

Met Asp Thr Ser Glu Asn Arg Pro Glu Asn Asp Val Pro Glu Pro Pro  
 1 5 10 15

Met Pro Ile Ala Asp Gln Val Ser Asn Asp Asp Arg Pro Glu Gly Ser  
 20 25 30

Val Glu Asp Glu Glu Lys Lys Glu Ser Ser Leu Pro Lys Ser Phe Lys  
 35 40 45

Arg Lys Ile Ser Val Val Ser Ala Thr Lys Gly Val Pro Ala Gly Asn  
 50 55 60

348

Ser Asp Thr Glu Gly Gly Gln Pro Gly Arg Lys Arg Arg Trp Gly Ala  
 65 70 75 80  
 Ser Thr Ala Thr Thr Gln Lys Lys Pro Ser Ile Ser Ile Thr Thr Glu  
 85 90 95  
 Ser Leu Lys Ser Leu Ile Pro Asp Ile Lys Pro Leu Ala Gly Gln Glu  
 100 105 110  
 Ala Val Val Asp Leu His Ala Asp Asp Ser Arg Ile Ser Glu Asp Glu  
 115 120 125  
 Thr Glu Arg Asn Gly Asp Asp Gly Thr His Asp Lys Gly Leu Lys Ile  
 130 135 140  
 Cys Arg Thr Val Thr Gln Val Val Pro Ala Glu Gly Gln Glu Asn Gly  
 145 150 155 160  
 Gln Arg Glu Glu Glu Glu Glu Lys Glu Pro Glu Ala Glu Pro Pro  
 165 170 175  
 Val Pro Pro Gln Val Ser Val Glu Val Ala Leu Pro Pro Pro Ala Glu  
 180 185 190  
 His Glu Val Lys Lys Val Thr Leu Gly Asp Thr Leu Thr Arg Arg Ser  
 195 200 205  
 Ile Ser Gln Gln Lys Ser Gly Val Ser Ile Thr Ile Asp Asp Pro Val  
 210 215 220  
 Arg Thr Ala Gln Val Pro Ser Pro Pro Arg Gly Lys Ile Ser Asn Ile  
 225 230 235 240  
 Val His Ile Ser Asn Leu Val Arg Pro Phe Thr Leu Gly Gln Leu Lys  
 245 250 255  
 Glu Leu Leu Gly Arg Thr Gly Thr Leu Val Glu Glu Ala Phe Trp Ile  
 260 265 270  
 Asp Lys Ile Lys Ser His Cys Phe Val Thr Tyr Ser Thr Val Glu Glu  
 275 280 285  
 Ala Val Ala Thr Arg Thr Ala Leu His Gly Val Lys Trp Pro Gln Ser  
 290 295 300  
 Asn Pro Lys Phe Leu Cys Ala Asp Tyr Ala Glu Gln Asp Glu Leu Asp  
 305 310 315 320  
 Tyr His Arg Gly Leu Leu Val Asp Arg Pro Ser Glu Thr Lys Thr Glu  
 325 330 335  
 Glu Gln Gly Ile Pro Arg Pro Leu His Pro Pro Pro Pro Pro Val  
 340 345 350  
 Gln Pro Pro Gln His Pro Arg Ala Glu Gln Arg Glu Gln Glu Arg Ala  
 355 360 365

349

Val Arg Glu Gln Trp Ala Glu Arg Glu Arg Glu Met Glu Arg Arg Glu  
 370 375 380  
 Arg Thr Arg Ser Glu Arg Glu Trp Asp Arg Asp Lys Val Arg Glu Gly  
 385 390 395 400  
 Pro Arg Ser Arg Ser Arg Ser Arg Xaa Arg Arg Arg Lys Glu Arg Ala  
 405 410 415  
 Lys Ser Lys Glu Lys Lys Ser Glu Lys Lys Glu Lys Ala Gln Glu Glu  
 420 425 430  
 Pro Pro Ala Lys Leu Leu Asp Asp Leu Phe Arg Lys Thr Lys Ala Ala  
 435 440 445  
 Pro Cys Ile Tyr Trp Leu Pro Leu Thr Asp Ser Gln Ile Val Gln Lys  
 450 455 460  
 Glu Ala Glu Arg Ala Glu Arg Ala Lys Glu Arg Glu Lys Arg Arg Lys  
 465 470 475 480  
 Glu Gln Glu Glu Glu Glu Gln Lys Glu Arg Glu Lys Glu Ala Glu Arg  
 485 490 495  
 Glu Arg Asn Arg Gln Leu Glu Arg Glu Lys Arg Arg Glu His Ser Arg  
 500 505 510  
 Glu Arg Asp Arg Glu Arg Glu Arg Glu Arg Glu Arg Asp Arg Gly Asp  
 515 520 525  
 Arg Asp Arg Asp Arg Glu Arg Asp Arg Glu Arg Gly Arg Glu Arg Asp  
 530 535 540  
 Arg Arg Asp Thr Lys Arg His Ser Arg Ser Arg Ser Arg Ser Thr Pro  
 545 550 555 560  
 Val Arg Asp Arg Gly Gly Arg  
 565

&lt;210&gt; 574

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 574

Glu Asn Asp Val Pro Glu Pro Pro Met Pro Ile Ala Asp Gln Val Ser  
 1 5 10 15  
 Asn Asp Asp Arg Pro Glu Gly Ser Val Glu Asp Glu Glu Lys Lys Glu  
 20 25 30  
 Ser Ser Leu Pro Lys Ser Phe Lys Arg Lys Ile Ser Val Val Ser Ala  
 35 40 45

350

<210> 575  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
 Val Asp Leu His Ala Asp Asp Ser Arg Ile Ser Glu Asp Glu Thr Glu  
           1                  5                  10                  15  
 Arg Asn Gly Asp Asp Gly Thr His Asp Lys Gly Leu Lys Ile Cys Arg  
                   20                  25                  30  
 Thr Val Thr Gln Val  
                   35

<210> 576  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<400> 576  
 Pro Gln Val Ser Val Glu Val Ala Leu Pro Pro Pro Ala Glu His Glu  
           1                  5                  10                  15  
 Val Lys Lys Val Thr Leu Gly Asp Thr Leu Thr Arg Arg Ser Ile Ser  
                   20                  25                  30  
 Gln Gln Lys Ser Gly Val Ser Ile Thr Ile Asp Asp Pro Val Arg Thr  
                   35                  40                  45  
 Ala Gln Val Pro Ser Pro Pro  
           50                  55

<210> 577  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<400> 577  
 Leu Lys Glu Leu Leu Gly Arg Thr Gly Thr Leu Val Glu Glu Ala Phe  
           1                  5                  10                  15  
 Trp Ile Asp Lys Ile Lys Ser His Cys Phe Val Thr Tyr Ser Thr Val  
                   20                  25                  30  
 Glu Glu Ala Val Ala Thr Arg Thr Ala Leu His Gly Val Lys Trp Pro  
                   35                  40                  45  
 Gln Ser Asn Pro Lys Phe Leu  
           50                  55

<210> 578  
 <211> 53  
 <212> PRT

351

&lt;213&gt; Homo sapiens

&lt;400&gt; 578

Val Asp Arg Pro Ser Glu Thr Lys Thr Glu Glu Gln Gly Ile Pro Arg  
 1 5 10 15

Pro Leu His Pro Pro Pro Pro Pro Val Gln Pro Pro Gln His Pro  
 20 25 30

Arg Ala Glu Gln Arg Glu Gln Glu Arg Ala Val Arg Glu Gln Trp Ala  
 35 40 45

Glu Arg Glu Arg Glu  
 50

&lt;210&gt; 579

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 579

Glu Trp Asp Arg Asp Lys Val Arg Glu Gly Pro Arg Ser Arg Ser Arg  
 1 5 10 15

Ser Arg Xaa Arg Arg Arg Lys Glu Arg Ala Lys Ser Lys Glu Lys Lys  
 20 25 30

Ser Glu Lys Lys Glu Lys Ala Gln Glu Glu Pro Pro Ala Lys Leu Leu  
 35 40 45

Asp Asp Leu Phe Arg Lys Thr Lys Ala Ala Pro  
 50 55

&lt;210&gt; 580

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 580

Pro Leu Thr Asp Ser Gln Ile Val Gln Lys Glu Ala Glu Arg Ala Glu  
 1 5 10 15

Arg Ala Lys Glu Arg Glu Lys Arg Arg Lys Glu Gln Glu Glu Glu  
 20 25 30

Gln Lys Glu Arg Glu Lys Glu Ala Glu Arg Glu Arg Asn Arg Gln Leu  
 35 40 45

Glu Arg Glu Lys Arg Arg Glu His Ser Arg Glu Arg Asp Arg Glu Arg  
 50 55 60

352

<210> 581  
<211> 32  
<212> PRT  
<213> Homo sapiens

<400> 581  
Leu Asp Val Pro Leu Ala Ser Arg Ser Pro Glu Phe Pro Leu Pro Leu  
1 5 10 15  
Met Thr Gln Ser Glu Leu Pro Arg Cys Pro Pro His Pro Gly Ala Arg  
20 25 30

<210> 582  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 582  
Leu Ala Thr Leu Ser Ile Ser Pro Ile Trp Ser Val Leu Ser Leu  
1 5 10 15

<210> 583  
<211> 51  
<212> PRT  
<213> Homo sapiens

<400> 583  
Gly Cys Asp Ser Cys Pro Pro His Leu Pro Arg Glu Ala Phe Ala Gln  
1 5 10 15  
Asp Thr Gln Ala Glu Gly Glu Cys Ser Ser Arg Ala Glu Arg Ala Asp  
20 25 30  
Met Cys Pro Asp Ala Pro Pro Ser Gln Glu Val Pro Glu Gly Pro Gly  
35 40 45  
Ala Ala Pro  
50

<210> 584  
<211> 91  
<212> PRT  
<213> Homo sapiens

<400> 584  
Arg Gly Trp Leu Pro Ser Ser Cys Leu Ser Cys Ala Leu Arg Val Cys  
1 5 10 15

353

Pro Asp Ser Ser Ser Thr Gln Ala Met Gly Met Leu Leu Ala Phe Trp  
                   20                  25                  30

Leu Pro Gly Ala Ser Trp Gln Glu Ala Ala Arg Gly Gln Tyr Ser Glu  
                   35                  40                  45

Asp Glu Asp Thr Asp Thr Asp Glu Tyr Lys Glu Ala Lys Ala Ser Ile  
                   50                  55                  60

Asn Pro Val Thr Gly Arg Val Glu Glu Lys Pro Pro Asn Pro Met Glu  
                   65                  70                  75                  80

Gly Met Thr Glu Glu Gln Lys Glu His Glu Ala  
                                   85                                  90

<210> 585  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 585  
 Thr Gln Ala Met Gly Met Leu Leu Ala Phe Trp Leu Pro Gly Ala Ser  
           1                  5                  10                  15

Trp Gln Glu Ala Ala Arg Gly Gln Tyr Ser Glu  
                   20                  25

<210> 586  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 586  
 Pro Gln Leu Pro Ser Cys Gly Arg Pro Trp Pro Gly Thr Ala Ser Val  
           1                  5                  10                  15

Phe Gln Ser His Thr Gln Gly Pro Arg Glu Asp Pro Asp Pro Cys Arg  
                   20                  25                  30

Ala Gln Gly Ser Ala Gly Thr His Cys Pro Ile Ser Leu Ser Pro Pro  
                   35                  40                  45

Arg Gln  
           50

<210> 587  
 <211> 103  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (23)  
 <223> Xaa equals any of the naturally occurring L-amino acids

354

<220>  
 <221> SITE  
 <222> (35)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 587  
 Lys Thr His Pro Arg Ala Leu Trp Ser Ala Gly Pro Ser Cys Ala Leu  
   1                  5                  10                  15  
 Cys Pro Gly Gly Ser Gly Xaa Thr Ser Pro Pro Gln Gly Ala Pro Arg  
                   20                  25                  30  
 Gly Ile Xaa Trp Asp Arg Cys Pro Gln Ile Gln Val Leu Glu Gly Gln  
           35                  40                  45  
 Arg Val Arg Phe Pro Ser Gln Pro Gln His Pro Ser His Leu Ala Pro  
       50                  55                  60  
 Arg Gly Gly Cys Gly Trp Arg Pro Asp Ser Arg Pro Leu Leu Pro Thr  
   65                  70                  75                  80  
 Pro Ser Gly Leu Ser Ser Phe Phe Pro Leu Asp Ala Gln Cys Trp Pro  
                   85                  90                  95  
 Trp Arg Thr Val Ser Trp Arg  
           100

<210> 588  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (40)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (174)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (186)  
 <223> Xaa equals any of the naturally occurring L-amino acids



355

&lt;400&gt; 588

Ala Gly Ala Pro Gly Gln Gln Ala Arg Leu Gln Tyr Leu Leu Ser Phe  
 1 5 10 15

Gln Gly Glu Gly Ala Pro His Glu Xaa Gly Ala Thr Gly Glu Gly Gly  
 20 25 30

Asp Gly Ala Trp Glu Ala Cys Xaa Cys Xaa Arg Cys Leu Leu Asn Trp  
 35 40 45

Gln Ala Gly Gly Trp Gly Leu Gln Leu Ser Leu Met Trp Leu His Arg  
 50 55 60

Gly Pro Leu Arg Pro Pro Gly Val Arg Trp Thr Pro Trp Ala Phe Leu  
 65 70 75 80

Glu Ala Cys Ser Trp Gly Pro Ala Leu Ser Leu Leu Gly Ser Gly His  
 85 90 95

Ser Leu Pro Gly Thr His Glu Gln Ala Ala Trp Ser Arg Gly Cys Gly  
 100 105 110

Gln His Gly Gln Ser Pro Thr Gln Lys Cys Lys Ser Ser Lys Glu Pro  
 115 120 125

Leu Ala Gln Ala Pro Pro Trp Asp Ser Pro Ala Ala Pro Pro His Gln  
 130 135 140

Gly Phe Ala Asp Val Leu Glu Arg Pro Thr Leu Glu Pro Phe Gly Val  
 145 150 155 160

Leu Ala Pro Pro Val Pro Ser Ala Leu Val Glu Ala Ala Xaa Gln Val  
 165 170 175

Leu Leu Arg Glu Pro Gln Gly Gly Phe Xaa Gly Thr Ala Ala His Arg  
 180 185 190

Ser Arg Cys Trp Lys Gly Ser Gly  
 195 200

&lt;210&gt; 589

&lt;211&gt; 145

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (81)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

356

&lt;222&gt; (125)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (142)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 589

Met Gln Leu Leu Phe Leu Leu Pro His Pro Ser Pro Gln Leu His Ala  
 1 5 10 15

Ser Leu Pro His Ser Ala Ala Leu Pro Cys Pro Arg Gly Glu Ser Leu  
 20 25 30

Thr Thr Ala Ser Pro Ala Gly Ala Ala Gly Arg Xaa Asp Ala Val Pro  
 35 40 45

Arg Cys Arg His Gln Ala Gly Arg Gly Trp Val Pro Arg Gly Pro Cys  
 50 55 60

Glu Arg Gly Gly Gly Asp Arg Gly Lys Pro Arg Ala Val Ala Trp Asp  
 65 70 75 80

Xaa Gly Ser Leu Arg Trp Ala Val Trp Ser Ala Arg Ala Gly Gln Gly  
 85 90 95

Arg Ser Ser Glu Pro Ala Pro Leu Ala Ser Arg Arg Gly Tyr Ser Thr  
 100 105 110

Cys Cys Leu Ser Arg Gly Lys Gly Leu Pro Met Arg Xaa Gly Arg Arg  
 115 120 125

Gly Arg Gly Val Met Val Pro Gly Lys Pro Ala Cys Ala Xaa Gly Ala  
 130 135 140

Cys  
 145

&lt;210&gt; 590

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 590

Gln His Pro Ser His Leu Ala Pro Arg Gly Gly Cys Gly Trp Arg Pro  
 1 5 10 15

Asp Ser Arg Pro Leu Leu Pro Thr Pro Ser Gly Leu Ser Ser Phe Phe  
 20 25 30

Pro Leu

&lt;210&gt; 591

&lt;211&gt; 30

357

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 591

Gly Val Arg Trp Thr Pro Trp Ala Phe Leu Glu Ala Cys Ser Trp Gly  
 1 5 10 15

Pro Ala Leu Ser Leu Leu Gly Ser Gly His Ser Leu Pro Gly  
 20 25 30

&lt;210&gt; 592

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 592

Trp Asp Ser Pro Ala Ala Pro Pro His Gln Gly Phe Ala Asp Val Leu  
 1 5 10 15

Glu Arg Pro Thr Leu Glu Pro Phe Gly Val Leu Ala  
 20 25

&lt;210&gt; 593

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 593

Arg Ser Ser Glu Pro Ala Pro Leu Ala Ser Arg Arg Gly Tyr Ser Thr  
 1 5 10 15

Cys Cys Leu Ser Arg Gly Lys Gly Leu Pro Met Arg  
 20 25

&lt;210&gt; 594

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 594

Pro Gly Phe Arg Gly Pro Ser Gly Ser Leu Gly Cys Ser Phe Phe Pro  
 1 5 10 15

Arg Ser Leu Gly Arg Val Leu Pro Pro Gly Cys Gln Arg Pro Gly Ala  
 20 25 30

His Ala Asp Ser Ser Pro Pro Pro Thr Pro  
 35 40

&lt;210&gt; 595

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

358

&lt;400&gt; 595

Glu Asp Leu Lys Lys Pro Asp Pro Ala Ser Leu Arg Ala Ala Ser Cys  
 1 5 10 15

Gly Glu Gly Lys Lys Arg Lys Ala Cys Lys Asn Cys Thr Cys Gly Leu  
 20 25 30

Ala Glu Glu Leu Glu Lys Glu Lys Ser Arg Glu Gln Met Ser Ser Gln  
 35 40 45

Pro Lys Ser Ala Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys  
 50 55 60

Ala Ser Cys Pro Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys  
 65 70 75 80

Val Leu Leu Ser

&lt;210&gt; 596

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 596

Glu Asp Leu Lys Lys Pro Asp Pro Ala Ser Leu Arg Ala Ala Ser Cys  
 1 5 10 15

Gly Glu Gly Lys Lys Arg Lys Ala Cys Lys Asn Cys Thr Cys Gly Leu  
 20 25 30

Ala Glu Glu Leu Glu Lys Glu Lys Ser Arg Glu Gln Met Ser Ser Gln  
 35 40 45

Pro Lys Ser Ala Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys  
 50 55 60

Ala Ser Cys Pro Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys  
 65 70 75 80

Val Leu Leu Ser Asp Ser Asn Leu His Asp  
 85 90

&lt;210&gt; 597

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 597

Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe Arg Cys Ala Ser Cys Pro  
 1 5 10 15

Tyr Leu Gly Met Pro Ala Phe Lys Pro Gly Glu Lys Val Leu Leu Ser  
 20 25 30

Asp Ser

359

<210> 598  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 598  
Ser Cys Gly Glu Gly Lys Lys Arg Lys Ala Cys Lys Asn Cys Thr Cys  
1 5 10 15  
Gly Leu Ala Glu Glu Leu Glu Lys Glu  
20 25

<210> 599  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 599  
Ser Gln Pro Lys Ser Ala Cys Gly Asn Cys Tyr Leu Gly Asp Ala Phe  
1 5 10 15  
Arg Cys Ala Ser Cys  
20

<210> 600  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 600  
Arg Glu Ala Gly Gln Asn Ser Glu Arg Gln Tyr Val Ser Leu Ser Arg  
1 5 10 15

Asp.

<210> 601  
<211> 16  
<212> PRT  
<213> Homo sapiens

<400> 601  
Cys Cys Cys Val Ser Lys Asp Gln Gly Ile Met Gly Pro Gly Phe Arg  
1 5 10 15

<210> 602  
<211> 103  
<212> PRT

360

&lt;213&gt; Homo sapiens

&lt;400&gt; 602

His Ser Val Thr Glu Leu Gln Thr Pro Ala Leu Ser Leu Ile Ser Ala  
 1 5 10 15

Met Leu Pro Pro Ser Cys Leu Ser Glu Leu Leu Val Tyr Ser Ile Leu  
 20 25 30

Cys Asp Thr Ser Gln Val Ala His Asn Leu Leu Arg Ala Pro Glu Asp  
 35 40 45

Ser Leu Thr Gly Cys Cys Asp Asp Ile Gln Cys Pro Ser Ala Pro Phe  
 50 55 60

His Pro Gln Pro His Leu Thr Val Ala Leu His Leu Cys Pro Val Val  
 65 70 75 80

Ile Tyr Val Asn Leu Gln Val Leu Asn Leu Leu His Ile Leu Thr Tyr  
 85 90 95

Leu Glu Ile Leu His Val Leu  
 100

&lt;210&gt; 603

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 603

Leu Leu Val Tyr Ser Ile Leu Cys Asp Thr Ser Gln Val Ala His Asn  
 1 5 10 15

Leu Leu Arg Ala Pro Glu Asp Ser  
 20

&lt;210&gt; 604

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 604

Leu Thr Val Ala Leu His Leu Cys Pro Val Val Ile Tyr Val Asn Leu  
 1 5 10 15

Gln Val Leu Asn Leu Leu His Ile Leu Thr  
 20 25

&lt;210&gt; 605

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 605

Phe Phe Asn Ala Leu Tyr Val Phe Arg Lys Pro Gln Ala Ile Phe Asp

361

1                    5                    10                    15  
 Ser Glu Lys Glu Asn Lys Arg Lys Asn Pro Thr Lys Tyr Asn Asn Pro  
                   20                    25                    30  
 Leu Arg Tyr Ile Tyr Phe Lys Val Lys Leu Ile Phe Gln Phe Ile Pro  
                   35                    40                    45  
 Leu Ala Asn Tyr Lys Ile Lys  
                   50                    55

&lt;210&gt; 606

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 606

Glu Ser Ser Gly Gln Ala Arg Thr Leu Ala Asp Pro Gly Pro Gly Trp  
 1                    5                    10                    15  
 Pro Arg Gln Gln Gly Met Cys Phe Gly Ser Leu Thr Gly Leu Ser Thr  
                   20                    25                    30  
 Thr Pro His Gly Phe Leu Thr Val Ser Ala Glu Ala Asp Pro Arg Leu  
                   35                    40                    45  
 Ile Glu Ser Leu Ser Gln Met Leu Ser Met Gly Phe Ser Asp Glu Gly  
                   50                    55                    60  
 Gly Trp Leu Thr Arg Leu Leu Gln Thr Lys Asn Tyr Asp Ile Gly Ala  
                   65                    70                    75                    80  
 Ala Leu Asp Thr Ile Gln Tyr Ser Lys His  
                   85                    90

&lt;210&gt; 607

&lt;211&gt; 100

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 607

Tyr Ser Met Val Tyr Ile Tyr His Ile Phe Phe Ile His Ser Leu Leu  
 1                    5                    10                    15  
 Asp Gly Gln Leu Gly Trp Phe His Ile Phe Ala Ile Val Ser Cys Ala  
                   20                    25                    30  
 Ala Pro Asp Ile Ile Phe Asn Ser Phe Ala Phe Ser Thr Tyr Ile Ser  
                   35                    40                    45  
 Lys Ser Cys Ser Phe Tyr Leu Gln Asn Val Ser Cys Ile His Ser Ser  
                   50                    55                    60  
 Leu Ser Ile Phe Asn Leu Phe Gln Cys Pro Ile Ile Ser Cys Met Glu  
                   65                    70                    75                    80

362

Glu Cys Asn Asn Trp Leu Thr Gly Leu Phe Leu His Phe Lys Ile Lys  
                     85                    90                    95

Arg Cys Asp Arg  
                     100

<210> 608  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<400> 608  
 Leu Ser Pro Ser Pro Arg Cys Cys Pro Trp Ala Ser Leu Met Lys Ala  
   1                    5                    10                    15

Ala Gly Ser Pro Gly Ser Cys Arg Pro Arg Thr Met Thr Ser Glu Arg  
                     20                    25                    30

Leu Trp Thr Pro Ser Ser Ile Gln Ser Ile Pro Arg Arg Cys Asp His  
                     35                    40                    45

Phe Cys Pro Pro Leu Leu Arg Ala Pro Leu Leu Ser His Ser Cys Val  
                     50                    55                    60

Lys Leu Ala  
                     65

<210> 609  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 609  
 Gly Trp Pro Arg Gln Gln Gly Met Cys Phe Gly Ser Leu Thr Gly Leu  
   1                    5                    10                    15

Ser Thr Thr Pro His Gly Phe Leu Thr Val Ser Ala Glu Ala Asp Pro  
                     20                    25                    30

Arg Leu

<210> 610  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 610  
 Leu Gly Trp Phe His Ile Phe Ala Ile Val Ser Cys Ala Ala Pro Asp  
   1                    5                    10                    15

Ile Ile Phe Asn Ser Phe Ala Phe Ser Thr Tyr Ile Ser Lys Ser Cys  
                     20                    25                    30

Ser



363

<210> 611  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 611  
 Ser Leu Ser Ile Phe Asn Leu Phe Gln Cys Pro Ile Ile Ser Cys Met  
           1                  5                  10                  15

Glu Glu Cys Asn Asn Trp Leu Thr Gly  
                   20                  25

<210> 612  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 612  
 Leu Met Lys Ala Ala Gly Ser Pro Gly Ser Cys Arg Pro Arg Thr Met  
           1                  5                  10                  15

Thr Ser Glu Arg Leu Trp Thr Pro Ser Ser Ile Gln Ser Ile  
                   20                  25                  30

<210> 613  
 <211> 152  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (35)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (71)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 613  
 Ser Ser Ser Ser Pro Arg Arg Pro Arg Glu Leu Leu Gly Ser Leu Lys  
           1                  5                  10                  15

Thr Pro Leu Val Arg Pro His Ser Ala Pro Leu Asp Leu Pro Gly Ser  
                   20                  25                  30

Phe Cys Xaa His Thr Ala Asp Pro Met Gly Ala Leu His Thr Arg Phe  
           35                  40                  45

Trp Gly Arg Gln Thr Trp Ile His Arg Lys Leu Arg Leu His Gly Thr  
           50                  55                  60

Ser Arg Leu Ala Ser Lys Xaa Gly Ile Gln Phe Leu Arg Asn Pro Ser

[illegible]

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<400> 614
Phe Leu Arg Asn Pro Ser Lys Thr His Thr Pro Arg Asp Ala Ala Phe
  1                      5                      10                      15
Arg Asp Pro Gly Gln Thr Pro Asp Pro Gln Ser Leu Gln Ala
                20                25                30

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<220>  
<221> SITE  
<222> (43)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (155)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 615  
Gln Glu Gly Ser Glu Pro Val Leu Leu Glu Gly Glu Cys Leu Val Val  
1 5 10 15  
Cys Glu Pro Gly Arg Ala Ala Ala Gly Gly Pro Gly Gly Ala Ala Leu  
20 25 30  
Gly Glu Ala Pro Pro Gly Arg Val Ala Phe Xaa Ala Val Arg Ser His  
35 40 45  
His His Glu Pro Ala Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile  
50 55 60

365

Tyr Phe Asp Gln Val Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala  
 65 70 75 80  
 Ser Gly Ser Phe Val Ala Pro Val Arg Gly Val Tyr Ser Phe Arg Phe  
 85 90 95  
 His Val Val Lys Val Tyr Asn Arg Gln Thr Val Gln Val Ser Leu Met  
 100 105 110  
 Leu Asn Thr Trp Pro Val Ile Ser Ala Phe Ala Asn Asp Pro Asp Val  
 115 120 125  
 Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu Pro Leu Asp Pro Gly  
 130 135 140  
 Asp Arg Val Ser Leu Arg Leu Arg Arg Gly Xaa Ser Thr Gly Trp  
 145 150 155

<210> 616  
 <211> 35  
 <212> PRT  
 <213> Homo sapiens

<400> 616  
 Gly Glu Thr Gly Asn Gly Thr Ser Gly Ala Ile Tyr Phe Asp Gln Val  
 1 5 10 15  
 Leu Val Asn Glu Gly Gly Gly Phe Asp Arg Ala Ser Gly Ser Phe Val  
 20 25 30  
 Ala Pro Val  
 35

<210> 617  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 617  
 Asn Asp Pro Asp Val Thr Arg Glu Ala Ala Thr Ser Ser Val Leu Leu  
 1 5 10 15  
 Pro Leu Asp Pro Gly Asp Arg Val Ser  
 20 25

<210> 618  
 <211> 11  
 <212> PRT  
 <213> Homo sapiens

<400> 618  
 Phe His Val Val Lys Val Tyr Asn Arg Gln Thr  
 1 5 10

366

&lt;210&gt; 619

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 619

Ile Tyr Phe Asp Gln Val Leu Val Asn

1

5

&lt;210&gt; 620

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 620

Glu Ser Arg Glu Arg Ser Gly Asn Arg Arg Gly Ala Glu Asp Arg Gly

1

5

10

15

Thr Cys Gly Leu Gln Ser Pro Ser Ala

20

25

&lt;210&gt; 621

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 621

Glu Met Pro Gln Phe Tyr Phe Phe Leu Lys Leu Gly Cys Leu Ala Gln

1

5

10

15

Val Pro Met Gln Arg Gly Gly Ile Gly Ala Arg Gly Ser Xaa Xaa Pro

20

25

30

Ala Xaa Ala Val Xaa Gly Ala Arg Glu Gly Arg Arg Lys Leu Ser Gly

35

40

45

367

Ala Gly Phe Leu Cys Leu Lys Asp Leu Gly Pro Ser Glu Arg Glu Asp  
 50 55 60

Glu Glu Ala Arg Glu Thr  
 65 70

&lt;210&gt; 622

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 622

Met Pro Gln Phe Tyr Phe Phe Leu Lys Leu Gly Cys Leu Ala Gln Val  
 1 5 10 15

Pro Met Gln Arg Gly Gly Ile Gly Ala Arg Gly  
 20 25

&lt;210&gt; 623

&lt;211&gt; 185

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 623

Gln Ala Thr Cys Ser Ala Ser Gly Ser Pro Gly Gln Phe Gly Gly Cys  
 1 5 10 15

Thr Pro Ser Pro His Gly Thr Gly Ser Cys Arg His Pro Gly Gln Gly  
 20 25 30

Leu Arg Arg Ser Gln Arg Pro Gly Gln Ser His Arg Pro Arg Ser Pro  
 35 40 45

Gly Pro Gly Arg Ser Arg Trp Pro His Trp Cys His Cys Arg Phe Pro  
 50 55 60

Leu Leu Ala His Gly Gly Gly Phe Gly Pro Gln Gln Met Pro Leu Ala  
 65 70 75 80

Gln Gly Val Pro Leu Pro Gly Leu Leu Pro Arg Ala Pro Leu Gln Gln  
 85 90 95

Leu Gly Gln Ala His Arg Pro Pro Gly Thr Pro Pro Pro Ala Gly Arg  
 100 105 110

Ala Leu Thr Pro Pro Gly Pro Thr Arg Pro Pro Gly Pro Glu Ala Pro  
 115 120 125

Glu Pro Arg Ala Ala Arg Asp Cys Val Gly Asp Leu Val Ala Ser Val  
 130 135 140

Ala Trp Leu Pro Thr Trp Leu Arg Gly Ser Ala Thr His Lys Cys Pro  
 145 150 155 160

Gly Leu Leu Pro Leu Phe Cys Phe Arg Ser Ser Pro Trp Ile Leu Thr

368

165

170

175

Ala Gly Thr Leu Ile Val Cys Pro Leu  
180 185

&lt;210&gt; 624

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 624

Gly Cys Thr Pro Ser Pro His Gly Thr Gly Ser Cys Arg His Pro Gly  
1 5 10 15

Gln Gly Leu Arg Arg Ser Gln Arg Pro  
20 25

&lt;210&gt; 625

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 625

Ser Arg Trp Pro His Trp Cys His Cys Arg Phe Pro Leu Leu Ala His  
1 5 10 15

Gly Gly Gly Phe Gly Pro Gln Gln Met Pro  
20 25

&lt;210&gt; 626

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 626

Asp Cys Val Gly Asp Leu Val Ala Ser Val Ala Trp Leu Pro Thr Trp  
1 5 10 15

Leu Arg Gly Ser Ala Thr His Lys Cys Pro Gly Leu  
20 25

&lt;210&gt; 627

&lt;211&gt; 115

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 627

Asp Asp Arg Pro Arg Val Gln His Gln Ala His Leu Asp Ser Leu Ala  
1 5 10 15

369

Val Val His Leu His His Met Glu Pro Glu Ala Val Asp Thr Pro Asp  
                   20                  25                  30

Arg Gly Tyr Glu Gly Ala Arg Gly Pro Val Lys Ala Thr Ala Leu Val  
                   35                  40                  45

His Gln Asp Leu Val Glu Val Asp Gly Pro Thr Gly Ala Ile Ala Gly  
                   50                  55                  60

Phe Pro Cys Trp Leu Met Val Val Ala Ser Asp Arg Xaa Lys Cys His  
                   65                  70                  75                  80

Ser Pro Arg Gly Cys Leu Ser Gln Gly Cys Ser Pro Gly Pro Pro Cys  
                   85                  90                  95

Ser Ser Ser Ala Arg Leu Thr Asp His Gln Ala Leu Pro Leu Gln Gln  
                   100                  105                  110

Asp Gly Leu  
                   115

<210> 628  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 628  
 Tyr Glu Gly Ala Arg Gly Pro Val Lys Ala Thr Ala Leu Val His Gln  
   1                  5                  10                  15

Asp Leu Val Glu Val Asp Gly Pro Thr Gly Ala Ile Ala Gly Phe  
                   20                  25                  30

<210> 629  
 <211> 159  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (22)  
 <223> Xaa equals any of the naturally occurring L-amino acids.

<400> 629  
 Met Ala Pro Leu Val Pro Leu Pro Val Ser Pro Ala Gly Ser Trp Trp  
   1                  5                  10                  15

Trp Leu Arg Thr Ala Xaa Asn Ala Thr Arg Pro Gly Gly Ala Ser Pro  
                   20                  25                  30

Arg Ala Ala Pro Pro Gly Pro Pro Ala Ala Ala Arg Pro Gly Ser Gln  
                   35                  40                  45

Thr Thr Arg His Ser Pro Ser Ser Arg Thr Gly Ser Asp Pro Ser Trp  
                   50                  55                  60

370

Ala His Pro Ala Pro Arg Ala Arg Ser Thr Arg Thr Lys Gly Ser Pro  
65 70 75 80

Gly Leu Cys Arg Gly Pro Gly Ser Gln Cys Gly Leu Ala Pro Asn Met  
85 90 95

Ala Glu Gly Leu Cys Asn Pro Gln Val Pro Arg Ser Ser Ala Pro Leu  
100 105 110

Leu Phe Pro Leu Leu Ser Leu Asp Ser His Arg Arg His Pro Asp Ser  
115 120 125

Leu Pro Ser Leu Gly Ser Leu Asn Pro Leu Ser Ile Pro Val Ser Gln  
130 135 140

Leu Cys Pro Ala Ser His Ser Tyr Ser Cys Cys His Cys Ser Ser  
145 150 155

&lt;210&gt; 630

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 630

Ser Ser Arg Thr Gly Ser Asp Pro Ser Trp Ala His Pro Ala Pro Arg  
1 5 10 15

Ala Arg Ser Thr Arg Thr Lys Gly Ser Pro Gly Leu Cys  
20 25

&lt;210&gt; 631

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 631

Arg Arg His Pro Asp Ser Leu Pro Ser Leu Gly Ser Leu Asn Pro Leu  
1 5 10 15

Ser Ile Pro Val Ser Gln Leu Cys Pro Ala Ser  
20 25

&lt;210&gt; 632

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 632

Ser Thr His Ala Ser Gly Pro Pro Ala Pro Glu Arg Leu Cys Leu Pro  
1 5 10 15

Glu Arg Gly Thr Ala Pro Trp Gly Arg Arg Ala Asn Asp Ala Ala  
20 25 30



371

<210> 633  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (60)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (83)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (84)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (165)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 633  
 Val Arg Arg Trp Trp Leu Arg Thr Met Gly Ala Ala Ala His Cys Thr  
   1                  5                  10                  15  
 Pro Glu Gln Arg Arg Pro Arg Arg Pro Ala Thr Ile Leu Gly Met Asp  
           20                  25                  30  
 Thr Gln Asn Ile Leu His Thr Arg Leu Ser Leu Cys Ser Leu Ser Trp  
       35                  40                  45  
 Val Ser Leu Ala Ser Ser Phe Xaa Xaa Leu Ala Xaa Arg Arg Lys Ala  
   50                  55                  60  
 Ile Val Val Gln Gln Lys Gln Ser Lys Ile Ser Lys Lys Lys Lys Val  
   65                  70                  75                  80  
 Glu Lys Xaa Xaa Leu Asn Asp Ser Val Asn Glu Asn Ser Asp Thr Val  
           85                  90                  95  
 Gly Gln Ile Val His Tyr Ile Met Lys Asn Glu Ala Asn Ala Asp Val  
       100                  105                  110

[illegible]

<400> 634  
Ile Met Lys Asn Glu Ala Asn Ala Asp Val Leu Lys Ala Met Val Ala  
1 5 10 15

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<210> 635
<211> 143
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (77)
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 635  
His Cys His Leu Trp Ala Ser Gly Ser Cys Leu Ala Cys Phe Phe Pro  
1 5 10 15

Gly Gly Leu Thr Arg Asp Ala Ala Gln Gln His Val Thr Lys Ser Tyr  
20 25 30

Ser Pro Pro Tyr Leu Ser Gln Thr Ser His Ser Cys Leu Val Phe Gln  
35 40 45

Pro Val Leu Trp Pro Glu Tyr Thr Phe Trp Asn Leu Phe Glu Ala Ile  
50 55 60

Leu Gln Phe Gln Met Asn His Ser Val Leu Gln Gln Xaa Gly Pro Arg  
65 70 75 80

His Val Cys Arg Gly Ala Glu Glu Ala Ala Ala Gly Glu Gly Pro Gly  
85 90 95

373

Tyr Ser Asp Arg Ala Ala Ala Ala Arg Gly Ala Pro Ser Gln Trp Gly  
 100 105 110

Arg Pro Ala Pro Lys Asp Thr Leu Ala Gln Thr Leu Gly Gln Thr Gly  
 115 120 125

Arg Ala Ser Pro Arg Leu Pro Ala Gly Leu Gly Thr Gln Ala Ser  
 130 135 140

&lt;210&gt; 636

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 636

Pro Ala Pro Lys Asp Thr Leu Ala Gln Thr Leu Gly Gln Thr Gly Arg  
 1 5 10 15

Ala Ser Pro Arg Leu Pro Ala Gly Leu Gly Thr Gln  
 20 25

&lt;210&gt; 637

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 637

Thr Ile Ala Cys Phe Ser Xaa Lys Ala Arg Asp Met Tyr Ala Glu Glu  
 1 5 10 15

Arg Lys Arg Gln Gln Leu Glu Arg Asp Gln Ala Thr Val Thr Glu Gln  
 20 25 30

Leu Leu Arg Glu Gly Leu Gln Ala Ser Gly Asp Ala Gln Leu Arg Arg  
 35 40 45

Thr Arg Leu His Lys Leu Ser Ala Arg Arg Glu Glu Arg Val Gln Gly  
 50 55 60

Phe Leu Gln Ala Leu Glu Leu Lys Arg Ala Asp Trp Leu Ala Arg Leu  
 65 70 75 80

Gly Thr Ala Ser Ala  
 85

&lt;210&gt; 638

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

374

&lt;400&gt; 638

Leu Arg Arg Thr Arg Leu His Lys Leu Ser Ala Arg Arg Glu Glu Arg  
 1 5 10 15

Val Gln Gly Phe Leu Gln Ala Leu Glu Leu Lys Arg  
 20 25

&lt;210&gt; 639

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 639

Lys Met Asn Ser Ile Pro Trp Gln Ile Pro Lys Ile Thr Pro Xaa Leu  
 1 5 10 15

Asp Ala Asn Leu Val Ile Val Glu Cys Lys Pro Leu Trp Phe Cys Ile  
 20 25 30

Gly Thr Ile Lys Gln Leu Lys Leu Trp Asn Gln Val Phe Met Gly Phe  
 35 40 45

Lys Ser Met Phe Phe Arg Ile Gly Lys Leu Asn Tyr Leu Phe Thr Ile  
 50 55 60

Pro Tyr Cys Tyr Leu Phe Ile Asp Asn Ile Leu Gly Ile Phe Tyr Ser  
 65 70 75 80

Ile Leu Gly Ala Gln Gly Ile Lys Tyr Asn Phe Tyr Ile Gln Arg Ile  
 85 90 95

Phe Thr Cys Leu Leu Asn Leu Asn Leu Lys Ile His Ser Asn Leu Ala  
 100 105 110

&lt;210&gt; 640

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 640

Leu Trp Phe Cys Ile Gly Thr Ile Lys Gln Leu Lys Leu Trp Asn Gln  
 1 5 10 15

Val Phe Met Gly Phe Lys Ser Met Phe Phe Arg  
 20 25

&lt;210&gt; 641

375

<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 641  
Tyr Ser Ile Leu Gly Ala Gln Gly Ile Lys Tyr Asn Phe Tyr Ile Gln  
1 5 10 15  
Arg Ile Phe Thr Cys Leu Leu Asn Leu Asn  
20 25

<210> 642  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 642  
Thr Phe Lys Leu Val Arg Phe Leu Glu  
1 5

<210> 643  
<211> 32  
<212> PRT  
<213> Homo sapiens

<400> 643  
Pro Arg Ser Arg Pro Ala Leu Arg Pro Gly Arg Gln Arg Pro Pro Ser  
1 5 10 15  
His Ser Ala Thr Ser Gly Val Leu Arg Pro Arg Lys Lys Pro Asp Pro  
20 25 30

<210> 644  
<211> 120  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (105)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (115)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 644  
Arg Lys Ser Phe Ala Lys Pro Val Leu Trp Thr Asn Ala Ile Gln Ala  
1 5 10 15  
Gly Arg Gly Arg Val Leu Cys Tyr Thr Arg Pro Pro Pro Ala Ser Ser

376

|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
|     | 20  |     | 25  |     | 30  |
| Ser | Phe | Ser | Ala | Leu | Val |
|     | 35  |     |     | 40  |     |
| Pro | Asp | Gly | Asn | Arg | Met |
|     |     |     |     |     | 45  |
| Glu | Gly | Leu | Arg |     |     |
| Thr | Tyr | Phe | Leu | Asn | Ala |
|     | 50  |     |     | 55  |     |
| Phe | Asp | Pro | Gly | Thr | Asp |
|     |     |     |     |     | 60  |
| Tyr | Leu | Tyr | Leu |     |     |
| Phe | Pro | Phe | Ser | Phe | Thr |
|     | 65  |     |     | 70  |     |
| Val | Thr | Phe | Gln | His | Cys |
|     |     |     |     | 75  |     |
| Leu | Thr | Val | Arg |     |     |
|     |     |     |     |     | 80  |
| Trp | Ala | Phe | Glu | Ser | Leu |
|     |     |     |     | 85  |     |
| Gln | Val | Pro | Gln | Asn | Arg |
|     |     |     |     | 90  |     |
| Pro | Glu | Arg | Trp |     |     |
|     |     |     |     |     | 95  |
| Ala | Ser | His | Pro | Leu | Pro |
|     |     |     |     | 100 |     |
| Thr | His | Xaa | Pro | Ala | Tyr |
|     |     |     |     | 105 |     |
| Leu | Pro | Asp | Asn |     |     |
|     |     |     |     |     | 110 |
| Gln | Val | Xaa | Met | Ser | Ala |
|     |     |     |     |     |     |
| Ser | Gly |     |     |     |     |
|     | 115 |     |     |     | 120 |

&lt;210&gt; 645

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 645

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Asn | Arg | Met | Glu | Gly | Leu | Arg | Thr | Tyr | Phe | Leu | Asn | Ala | Phe | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     | 15  |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Gly | Thr | Asp | Tyr | Leu | Tyr | Leu | Phe |
|     |     |     | 20  |     |     |     |     | 25  |

&lt;210&gt; 646

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 646

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Gln | His | Cys | Leu | Thr | Val | Arg | Trp | Ala | Phe | Glu | Ser | Leu | Gln | Val |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Gln | Asn | Arg | Pro | Glu | Arg | Trp | Ala | Ser | His | Pro | Leu | Pro |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |

&lt;210&gt; 647

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

377

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 647

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Thr | Leu | Ile | Thr | Pro | Ser | Xaa | Lys | Leu | Thr | Phe | Xaa | Lys | Gly | Asn |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ser | Trp | Ser | Ser | Arg | Ala | Cys | Ser | Ser | Thr | Leu | Val | Asp | Pro |
|     | 20  |     |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

&lt;210&gt; 648

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 648

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Phe | Leu | His | Ala | Val | Asp | Pro | Trp | Pro | Ser | Asn | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     |

&lt;210&gt; 649

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 649

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Ser | Cys | Gln | Ser | Gly | Val | Phe | Leu | Val | Phe | Thr | Gly | Cys | Ser | Val |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Cys | Gln | Met | Leu | Ser | Gly | Ala | Val | Val | Val | Trp | Arg | Arg | Ser | Ala |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Asp | Ser | Ala | Val | Trp | Gln | Ala | Ser | Ile | Asn | Lys | Pro | Arg | Gly |
|     |     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Arg | His | Gly | Ile | Lys | Gly | Glu | Asn | Thr | Ser | Val |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |

&lt;210&gt; 650

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 650

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Val | Phe | Thr | Gly | Cys | Ser | Val | Leu | Cys | Gln | Met | Leu | Ser | Gly | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Val | Trp | Arg | Arg | Ser | Ala | Pro | Glu | Asp | Ser | Ala | Val | Trp | Gln |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |
|-----|-----|-----|
| Ala | Ser | Ile |
|     | 35  |     |

&lt;210&gt; 651

378

<211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 651  
 Gly His Pro Ser Pro Ala Leu Ser Ile Ala Pro Ser Asp Gly Ser Gln  
     1                    5                    10                    15  
 Leu Pro Cys Asp Glu Val Pro Tyr Gly Glu Ala His Val Thr Arg Tyr  
           20                    25                    30  
 Cys Lys Lys Pro Leu Thr Asn Ser His Leu Glu Thr Glu Ala Gln Ser  
           35                    40                    45  
 Ser Ser Leu  
     50

<210> 652  
 <211> 151  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (131)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (145)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 652  
 Asn Asn Lys His Tyr Leu Ser Phe Cys Gly Ser Gly Phe Cys Pro Val  
     1                    5                    10                    15  
 Tyr Leu Gly Phe Thr Gly Leu Ala Ser His Gln Ala Val Lys Val Leu  
           20                    25                    30  
 Val Val Ala Val Ile Ile Pro Arg Gln Asp Arg Glu Arg Ile Cys Leu  
           35                    40                    45  
 Gln Ala Gln Val Gly Arg Ile His Leu Arg Gly Cys Trp Thr Gly Pro  
     50                    55                    60  
 Pro Phe Leu Asp Gly Tyr Trp Ser Glu Ala Phe Tyr Asn Thr Leu Ser  
     65                    70                    75                    80  
 Arg Gly Pro Leu His Arg Ala Pro His His Met Ala Thr Gly Phe His  
           85                    90                    95  
 Gln Arg Glu Gln Trp Lys Glu Gln Glu Lys Gly Asp Gln Gly Arg His  
           100                    105                    110  
 Arg Ser Leu Leu Val Ala Ser Pro Gln Lys Arg Cys Tyr Phe Cys Cys  
     115                    120                    125



379

Ile Leu Xaa Val Arg Ser Glu Ser Leu Gly Pro Gly Val Glu Phe Tyr  
 130 135 140

Xaa Gly Val Asn Gly Arg Arg  
 145 150

<210> 653  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 653  
 Glu Arg Ile Cys Leu Gln Ala Gln Val Gly Arg Ile His Leu Arg Gly  
 1 5 10 15

Cys Trp Thr Gly Pro Pro Phe Leu Asp Gly Tyr Trp Ser Glu Ala Phe  
 20 25 30

<210> 654  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 654  
 Ser Asp Gly Ser Gln Leu Pro Cys Asp Glu Val Pro Tyr Gly Glu Ala  
 1 5 10 15

His Val Thr Arg Tyr Cys Lys Lys Pro Leu  
 20 25

<210> 655  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 655  
 His Gln Arg Glu Gln Trp Lys Glu Gln Glu Lys Gly Asp Gln Gly Arg  
 1 5 10 15

His Arg Ser Leu Leu Val Ala Ser Pro Gln Lys  
 20 25

<210> 656  
 <211> 263  
 <212> DNA  
 <213> Homo sapiens

<400> 656  
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgcctg gagccagtcc caccacgctc 60  
 gcgtttcctc ctgtagtgct cacaggcccc agcaccgatg gcattccctt tgccctgagt 120

380

ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180  
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240  
 aagtattaaa agtagctttg taa 263

<210> 657  
 <211> 263  
 <212> DNA  
 <213> Homo sapiens

<400> 657  
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgcctg gagccagtcc caccacgctc 60  
 gcgtttcctc ctgtagtgct cacaggtccc agcaccgatg gcattccctt tgcctgagt 120  
 ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180  
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240  
 aagtattaaa agtagctttg taa 263

<210> 658  
 <211> 263  
 <212> DNA  
 <213> Homo sapiens

<400> 658  
 gcttcgtgtc caaccctctt gcccttcgcc tgtgtgcctg gagccagtcc caccacgctc 60  
 gcgtttcctc ctgtagtgct cacaggtccc agcaccgatg gcattccctt tgcctgagt 120  
 ctgcagcggg tcccttttgt gcttccttcc cctcaggtag cctctctccc cctgggccac 180  
 tcccgggggt gaggggggta ccccttccca gtgtttttta ttctgtggg gctcacccca 240  
 aagtattaaa agtagctttg taa 263

<210> 659  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 659  
 Phe Arg Ile Asn Arg Leu Thr Ile Gly Xaa Ala Val Ala Met Thr Arg  
 1 5 10 15

381

Gly Asn Gln Arg Glu Leu Ala Arg Gln Lys Asn Met Lys Lys Gln Ser  
                   20                  25                  30

Asp Ser Val Lys Gly Lys Arg Arg Asp Asp Gly Leu Ser Ala Ala Ala  
           35                  40                  45

Arg Lys Gln Arg Asp Ser Glu Ile  
       50                  55

&lt;210&gt; 660

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Ala Val Ala Met Thr Arg Gly Asn Gln Arg Glu Leu Ala Arg Gln Lys  
       1                  5                  10                  15

Asn Met Lys Lys Gln Ser Asp Ser Val Lys Gly Lys Arg  
           20                  25

&lt;210&gt; 661

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 661

Lys Ser Arg Ala Thr Arg Leu Arg Glu Ser Ala Glu Met Thr Gly Phe  
       1                  5                  10                  15

Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser Cys Ser Arg Ser  
           20                  25                  30

Arg Lys Arg Gln Thr Arg Arg Arg Arg Asn Pro Ser Ser Phe Val Ala  
           35                  40                  45

Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro Gly Ala Ser Pro  
           50                  55                  60

Thr Thr Leu Ala Phe Pro Pro Val Val Leu Thr Gly Pro Ser Thr Asp  
       65                  70                  75                  80

Gly Ile Pro Phe Ala Leu Ser Leu Gln Arg Val Pro Phe Val Leu Pro  
           85                  90                  95

Ser Pro Gln Val Ala Ser Leu Pro Leu Gly His Ser Arg Gly  
           100                  105                  110

&lt;210&gt; 662

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 662

382

Leu Arg Glu Ser Ala Glu Met Thr Gly Phe Leu Leu Pro Pro Ala Ser  
1 5 10 15

Arg Gly Thr Arg Arg Ser Cys Ser Arg Ser  
20 25

&lt;210&gt; 663

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 663

Val Val Leu Thr Gly Pro Ser Thr Asp Gly Ile Pro Phe Ala Leu Ser  
1 5 10 15

Leu Gln Arg Val Pro Phe Val Leu Pro Ser Pro Gln Val Ala  
20 25 30

&lt;210&gt; 664

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 664

Leu Leu Ser Thr Ser His Leu Leu Thr Gln Ser Tyr Ser Phe Asn Lys  
1 5 10 15

Arg Ser His Ser Phe Ala Trp Lys Asn Ala His Cys Ile Leu Gln Ser  
20 25 30

Glu Asn Asn Glu Leu Gln Asn Ser Val Tyr Ile Tyr Val Cys Ile Tyr  
35 40 45

Val His Phe Ile Cys Thr Phe Leu Cys Asp Ile  
50 55

&lt;210&gt; 665

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 665

Lys Arg Ser His Ser Phe Ala Trp Lys Asn Ala His Cys Ile Leu Gln  
1 5 10 15

Ser Glu Asn Asn Glu Leu Gln Asn Ser Val Tyr Ile Tyr Val Cys Ile  
20 25 30

&lt;210&gt; 666

&lt;211&gt; 160

&lt;212&gt; DNA

383

&lt;213&gt; Homo sapiens

&lt;400&gt; 666

```

tggtcactg tttacaatc actgctgtgg aatcatgata ccacttttag ctctttgcat      60
cttccttcag tgtatttttg tttttcaaga ggaagtagat tttaactgga caactttgag      120
tactgacatc attgataaat aaactggcctt gtggtttcaa                          160

```

&lt;210&gt; 667

&lt;211&gt; 292

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (105)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 667

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Leu Asp Glu Leu Met Ala His Leu Thr Glu Met Gln Ala Lys Val Ala
 1              5              10              15

Val Arg Ala Asp Ala Gly Lys Lys His Leu Pro Asp Lys Gln Asp His
      20              25              30

Lys Ala Ser Leu Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln
      35              40              45

Asp Leu Gly Ile Ala Thr Val Pro Lys Gly His Cys Ala Ser Cys Gln
      50              55              60

Lys Pro Ile Ala Gly Lys Val Ile His Ala Leu Gly Gln Ser Trp His
      65              70              75              80

Pro Glu His Phe Val Cys Thr His Cys Lys Glu Glu Ile Gly Ser Ser
      85              90              95

Pro Phe Phe Glu Arg Ser Gly Leu Xaa Tyr Cys Pro Asn Asp Tyr His
      100             105             110

Gln Leu Phe Ser Pro Arg Cys Ala Tyr Cys Ala Ala Pro Ile Leu Asp
      115             120             125

Lys Val Leu Thr Ala Met Asn Gln Thr Trp His Pro Glu His Phe Phe
      130             135             140

Cys Ser His Cys Gly Glu Val Phe Gly Ala Glu Gly Phe His Glu Lys
      145             150             155             160

Asp Lys Lys Pro Tyr Cys Arg Lys Asp Phe Leu Ala Met Phe Ser Pro
      165             170             175

Lys Cys Gly Gly Cys Asn Arg Pro Val Leu Glu Asn Tyr Leu Ser Ala
      180             185             190

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384

Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys Gly Asp Cys Phe  
 195 200 205

Thr Ser Phe Ser Thr Gly Ser Phe Phe Glu Leu Asp Gly Arg Pro Phe  
 210 215 220

Cys Glu Leu His Tyr His His Arg Arg Gly Thr Leu Cys His Gly Cys  
 225 230 235 240

Gly Gln Pro Ile Thr Gly Arg Cys Ile Ser Ala Met Gly Tyr Lys Phe  
 245 250 255

His Pro Glu His Phe Val Cys Ala Phe Cys Leu Thr Gln Leu Ser Lys  
 260 265 270

Gly Ile Phe Arg Glu Gln Asn Asp Lys Thr Tyr Cys Gln Pro Cys Phe  
 275 280 285

Asn Lys Leu\*Phe  
 290

<210> 668  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<400> 668  
 Lys Ala Ser Leu Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln  
 1 5 10 15

Asp Leu Gly Ile Ala Thr Val Pro Lys Gly His Cys Ala Ser Cys Gln  
 20 25 30

Lys Pro Ile Ala Gly Lys Val Ile His Ala Leu  
 35 40

<210> 669  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 669  
 Cys Pro Asn Asp Tyr His Gln Leu Phe Ser Pro Arg Cys Ala Tyr Cys  
 1 5 10 15

Ala Ala Pro Ile Leu Asp Lys Val Leu Thr Ala Met Asn Gln Thr Trp  
 20 25 30

His Pro Glu His Phe Phe Cys Ser His Cys Gly Glu Val Phe Gly Ala  
 35 40 45

Glu Gly  
 50

<210> 670

385

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 670

Asp Lys Lys Pro Tyr Cys Arg Lys Asp Phe Leu Ala Met Phe Ser Pro  
 1 5 10 15

Lys Cys Gly Gly Cys Asn Arg Pro Val Leu Glu Asn Tyr Leu Ser Ala  
 20 25 30

Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys Gly Asp Cys Phe  
 35 40 45

Thr Ser Phe Ser Thr Gly Ser Phe Phe Glu Leu Asp Gly Arg Pro Phe  
 50 55 60

Cys Glu Leu  
 65

&lt;210&gt; 671

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Cys Gly Gln Pro Ile Thr Gly Arg Cys Ile Ser Ala Met Gly Tyr Lys  
 1 5 10 15

Phe His Pro Glu His Phe Val Cys Ala Phe Cys Leu Thr Gln Leu Ser  
 20 25 30

Lys Gly Ile Phe Arg Glu Gln Asn Asp Lys Thr Tyr Cys Gln  
 35 40 45

&lt;210&gt; 672

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (145)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 672

His Lys Ser Leu Ala Gly Ala Xaa Val Tyr Thr Thr Asn Ile Gln Glu  
 1 5 10 15

Leu Asn Val Tyr Ser Glu Ala Gln Glu Pro Lys Glu Ser Pro Pro Pro  
 20 25 30

386

Ser Lys Thr Ser Ala Ala Ala Gln Leu Asp Glu Leu Met Ala His Leu  
 35 40 45  
 Thr Glu Met Gln Ala Lys Val Ala Val Arg Ala Asp Ala Gly Lys Lys  
 50 55 60  
 His Leu Pro Asp Lys Gln Asp His Lys Ala Ser Leu Asp Ser Met Leu  
 65 70 75 80  
 Gly Gly Leu Glu Gln Glu Leu Gln Asp Leu Gly Ile Ala Thr Val Pro  
 85 90 95  
 Lys Gly His Cys Ala Ser Cys Gln Lys Pro Ile Ala Gly Lys Val Ile  
 100 105 110  
 His Ala Leu Gly Gln Ser Trp His Pro Glu His Phe Val Cys Thr His  
 115 120 125  
 Cys Lys Glu Glu Ile Gly Ser Ser Pro Phe Phe Glu Arg Ser Gly Leu  
 130 135 140  
 Xaa Tyr Cys Pro Asn Asp Tyr His Gln Leu Phe Ser Pro Arg Cys Ala  
 145 150 155 160  
 Tyr Cys Ala Ala Pro Ile Leu Asp Lys Val Leu Thr Ala Met Asn Gln  
 165 170 175  
 Thr Trp His Pro Glu His Phe Phe Cys Ser His Cys Gly Glu Val Phe  
 180 185 190  
 Gly Ala Glu Gly Phe His Glu Lys Asp Lys Lys Pro Tyr Cys Arg Lys  
 195 200 205  
 Asp Phe Leu Ala Met Phe Ser Pro Lys Cys Gly Gly Cys Asn Arg Pro  
 210 215 220  
 Val Leu Glu Asn Tyr Leu Ser Ala Met Asp Thr Val Trp His Pro Glu  
 225 230 235 240  
 Cys Phe Val Cys Gly Asp Cys Phe Thr Ser Phe Ser Thr Gly Ser Phe  
 245 250 255  
 Phe Glu Leu Asp Gly Arg Pro Phe Cys Glu Leu His Tyr His His Arg  
 260 265 270  
 Arg Gly Thr Leu Cys His Gly Cys Gly Gln Pro Ile Thr Gly Arg Cys  
 275 280 285  
 Ile Ser Ala Met Gly Tyr Lys Phe His Pro Glu His Phe Val Cys Ala  
 290 295 300  
 Phe Cys Leu Thr Gln Leu Ser Lys Gly Ile Phe Arg Glu Gln Asn Asp  
 305 310 315 320  
 Lys Thr Tyr Cys Gln Pro Cys Phe Asn Lys Leu Phe Pro Leu  
 325 330



387

<210> 673  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 673  
Asn Val Tyr Ser Glu Ala Gln Glu Pro Lys Glu Ser Pro Pro Pro Ser  
1 5 10 15

Lys Thr Ser Ala Ala Ala  
20

<210> 674  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 674  
Asp Ser Met Leu Gly Gly Leu Glu Gln Glu Leu Gln Asp Leu Gly Ile  
1 5 10 15

Ala Thr Val Pro Lys Gly His Cys Ala Ser  
20 25

<210> 675  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 675  
Tyr Leu Ser Ala Met Asp Thr Val Trp His Pro Glu Cys Phe Val Cys  
1 5 10 15

Gly Asp Cys Phe Thr Ser Phe Ser Thr Gly  
20 25

<210> 676  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 676  
Arg Cys Ile Ser Ala Met Gly Tyr Lys Phe His Pro Glu His Phe Val  
1 5 10 15

Cys Ala Phe Cys Leu Thr Gln Leu Ser Lys  
20 25

<210> 677  
<211> 127  
<212> PRT  
<213> Homo sapiens

388

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 677

Pro Thr Arg Pro Val Leu Phe Phe Ser Thr Cys Gln Ser Cys Ser Ser  
 1 5 10 15

Arg Pro Val Arg Gln Glu His Leu Gly Cys Arg Thr Met Glu Glu Leu  
 20 25 30

Asp Ala Leu Leu Glu Glu Leu Glu Arg Ser Thr Leu Gln Asp Ser Asp  
 35 40 45

Glu Tyr Ser Asn Pro Ala Pro Leu Pro Leu Asp Gln His Ser Arg Lys  
 50 55 60

Glu Thr Asn Leu Asp Glu Thr Ser Glu Ile Leu Ser Ile Gln Asp Asn  
 65 70 75 80

Thr Ser Pro Leu Pro Ala Xaa Ser Cys Ile Leu Pro Ile Ser Arg Ser  
 85 90 95

Ser Met Ser Thr Val Lys Pro Lys Ser Gln Arg Asn His His His Leu  
 100 105 110

Leu Lys Arg Gln Gln Leu Leu Ser Trp Met Ser Ser Trp Leu Thr  
 115 120 125

&lt;210&gt; 678

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 678

Pro Val Arg Gln Glu His Leu Gly Cys Arg Thr Met Glu Glu Leu Asp  
 1 5 10 15

Ala Leu Leu Glu Glu Leu Glu Arg Ser Thr Leu Gln  
 20 25

&lt;210&gt; 679

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 679

Ser Cys Ile Leu Pro Ile Ser Arg Ser Ser Met Ser Thr Val Lys Pro  
 1 5 10 15

Lys Ser Gln Arg Asn  
 20

&lt;210&gt; 680

389

<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 680  
Trp His Pro Glu His Phe Val Cys Thr His Cys  
1 5 10

<210> 681  
<211> 6  
<212> PRT  
<213> Homo sapiens

<400> 681  
Leu Phe Ser Pro Arg Cys  
1 5

<210> 682  
<211> 6  
<212> PRT  
<213> Homo sapiens

<400> 682  
Pro Ile Leu Asp Lys Val  
1 5

<210> 683  
<211> 8  
<212> PRT  
<213> Homo sapiens

<400> 683  
Thr Trp His Pro Glu His Phe Phe  
1 5

<210> 684  
<211> 7  
<212> PRT  
<213> Homo sapiens

<400> 684  
Glu Gly Phe His Glu Lys Asp  
1 5

<210> 685  
<211> 13  
<212> PRT  
<213> Homo sapiens

<400> 685  
Lys Phe His Pro Glu His Phe Val Cys Ala Phe Cys Leu  
1 5 10

390

&lt;210&gt; 686

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 686

Pro Ile Thr Gly Arg Cys Ile

1

5

&lt;210&gt; 687

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 687

His Pro Glu His Phe Val Cys

1

5

&lt;210&gt; 688

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 688

Arg Ile Tyr Cys Ser Glu Asp Thr Phe Ser Pro Xaa Ala Glu Ser Gly

1

5

10

15

Val Ser Trp Gln Ser Ser Val Ser Gln Leu Tyr Gln Asp Tyr Glu

20

25

30

&lt;210&gt; 689

&lt;211&gt; 452

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (61)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 689

Met Gly Ser Ser Gln Ser Val Glu Ile Pro Gly Gly Gly Thr Glu Gly

1

5

10

15

Tyr His Val Leu Arg Val Gln Glu Asn Ser Pro Gly His Arg Ala Gly

20

25

30

Leu Glu Pro Phe Phe Asp Phe Ile Val Ser Ile Asn Gly Ser Arg Leu

35

40

45

391

Asn Lys Asp Asn Asp Thr Leu Lys Asp Leu Leu Lys Xaa Asn Val Glu  
 50 55 60  
 Lys Pro Val Lys Met Leu Ile Tyr Ser Ser Lys Thr Leu Glu Leu Arg  
 65 70 75 80  
 Glu Thr Ser Val Thr Pro Ser Asn Leu Trp Gly Gly Gln Gly Leu Leu  
 85 90 95  
 Gly Val Ser Ile Arg Phe Cys Ser Phe Asp Gly Ala Asn Glu Asn Val  
 100 105 110  
 Trp His Val Leu Glu Val Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly  
 115 120 125  
 Leu Arg Pro His Ser Asp Tyr Ile Ile Gly Ala Asp Thr Val Met Asn  
 130 135 140  
 Glu Ser Glu Asp Leu Phe Ser Leu Ile Glu Thr His Glu Ala Lys Pro  
 145 150 155 160  
 Leu Lys Leu Tyr Val Tyr Asn Thr Asp Thr Asp Asn Cys Arg Glu Val  
 165 170 175  
 Ile Ile Thr Pro Asn Ser Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys  
 180 185 190  
 Gly Ile Gly Tyr Gly Tyr Leu His Arg Ile Pro Thr Arg Pro Phe Glu  
 195 200 205  
 Glu Gly Lys Lys Ile Ser Leu Pro Gly Gln Met Ala Gly Thr Pro Ile  
 210 215 220  
 Thr Pro Leu Lys Asp Gly Phe Thr Glu Val Gln Leu Ser Ser Val Asn  
 225 230 235 240  
 Pro Pro Ser Leu Ser Pro Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu  
 245 250 255  
 Thr Gly Leu Ser Ile Ser Ser Thr Pro Pro Ala Val Ser Ser Val Leu  
 260 265 270  
 Ser Thr Gly Val Pro Thr Val Pro Leu Leu Pro Pro Gln Val Asn Gln  
 275 280 285  
 Ser Leu Thr Ser Val Pro Pro Met Asn Pro Ala Thr Thr Leu Pro Gly  
 290 295 300  
 Leu Met Pro Leu Pro Ala Gly Leu Pro Asn Leu Pro Asn Leu Asn Leu  
 305 310 315 320  
 Asn Leu Pro Ala Pro His Ile Met Pro Gly Val Gly Leu Pro Glu Leu  
 325 330 335  
 Val Asn Pro Gly Leu Pro Pro Leu Pro Ser Met Pro Pro Arg Asn Leu  
 340 345 350

392

Pro Gly Ile Ala Pro Leu Pro Leu Pro Ser Glu Phe Leu Pro Ser Phe  
 355 360 365

Pro Leu Val Pro Glu Ser Ser Ser Ala Ala Ser Ser Gly Glu Leu Leu  
 370 375 380

Ser Ser Leu Pro Pro Thr Ser Asn Ala Pro Ser Asp Pro Ala Thr Thr  
 385 390 395 400

Thr Ala Lys Ala Asp Ala Ala Ser Ser Leu Thr Val Asp Val Thr Pro  
 405 410 415

Pro Thr Ala Lys Ala Pro Thr Thr Val Glu Asp Arg Val Gly Asp Ser  
 420 425 430

Thr Pro Val Ser Glu Lys Pro Val Ser Ala Ala Val Asp Ala Asn Ala  
 435 440 445

Ser Glu Ser Pro  
 450

<210> 690  
 <211> 109  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 690  
 Ser Val Glu Ile Pro Gly Gly Gly Thr Glu Gly Tyr His Val Leu Arg  
 1 5 10 15

Val Gln Glu Asn Ser Pro Gly His Arg Ala Gly Leu Glu Pro Phe Phe  
 20 25 30

Asp Phe Ile Val Ser Ile Asn Gly Ser Arg Leu Asn Lys Asp Asn Asp  
 35 40 45

Thr Leu Lys Asp Leu Leu Lys Xaa Asn Val Glu Lys Pro Val Lys Met  
 50 55 60

Leu Ile Tyr Ser Ser Lys Thr Leu Glu Leu Arg Glu Thr Ser Val Thr  
 65 70 75 80

Pro Ser Asn Leu Trp Gly Gly Gln Gly Leu Leu Gly Val Ser Ile Arg  
 85 90 95

Phe Cys Ser Phe Asp Gly Ala Asn Glu Asn Val Trp His  
 100 105

<210> 691  
 <211> 145  
 <212> PRT

393

&lt;213&gt; Homo sapiens

&lt;400&gt; 691

Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro His Ser Asp  
 1 5 10 15  
 Tyr Ile Ile Gly Ala Asp Thr Val Met Asn Glu Ser Glu Asp Leu Phe  
 20 25 30  
 Ser Leu Ile Glu Thr His Glu Ala Lys Pro Leu Lys Leu Tyr Val Tyr  
 35 40 45  
 Asn Thr Asp Thr Asp Asn Cys Arg Glu Val Ile Ile Thr Pro Asn Ser  
 50 55 60  
 Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr  
 65 70 75 80  
 Leu His Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser  
 85 90 95  
 Leu Pro Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly  
 100 105 110  
 Phe Thr Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro  
 115 120 125  
 Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser  
 130 135 140  
 Ser  
 145

&lt;210&gt; 692

&lt;211&gt; 145

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 692

Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro His Ser Asp  
 1 5 10 15  
 Tyr Ile Ile Gly Ala Asp Thr Val Met Asn Glu Ser Glu Asp Leu Phe  
 20 25 30  
 Ser Leu Ile Glu Thr His Glu Ala Lys Pro Leu Lys Leu Tyr Val Tyr  
 35 40 45  
 Asn Thr Asp Thr Asp Asn Cys Arg Glu Val Ile Ile Thr Pro Asn Ser  
 50 55 60  
 Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr  
 65 70 75 80  
 Leu His Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser  
 85 90 95

394

Leu Pro Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly  
 100 105 110

Phe Thr Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro  
 115 120 125

Pro Gly Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser  
 130 135 140

Ser  
 145

<210> 693  
 <211> 151  
 <212> PRT  
 <213> Homo sapiens

<400> 693  
 Arg Ile Pro Thr Arg Pro Phe Glu Glu Gly Lys Lys Ile Ser Leu Pro  
 1 5 10 15

Gly Gln Met Ala Gly Thr Pro Ile Thr Pro Leu Lys Asp Gly Phe Thr  
 20 25 30

Glu Val Gln Leu Ser Ser Val Asn Pro Pro Ser Leu Ser Pro Pro Gly  
 35 40 45

Thr Thr Gly Ile Glu Gln Ser Leu Thr Gly Leu Ser Ile Ser Ser Thr  
 50 55 60

Pro Pro Ala Val Ser Ser Val Leu Ser Thr Gly Val Pro Thr Val Pro  
 65 70 75 80

Leu Leu Pro Pro Gln Val Asn Gln Ser Leu Thr Ser Val Pro Pro Met  
 85 90 95

Asn Pro Ala Thr Thr Leu Pro Gly Leu Met Pro Leu Pro Ala Gly Leu  
 100 105 110

Pro Asn Leu Pro Asn Leu Asn Leu Asn Leu Pro Ala Pro His Ile Met  
 115 120 125

Pro Gly Val Gly Leu Pro Glu Leu Val Asn Pro Gly Leu Pro Pro Leu  
 130 135 140

Pro Ser Met Pro Pro Arg Asn  
 145 150

<210> 694  
 <211> 109  
 <212> PRT  
 <213> Homo sapiens

<400> 694  
 Pro Gly Leu Pro Pro Leu Pro Ser Met Pro Pro Arg Asn Leu Pro Gly  
 1 5 10 15



395

Ile Ala Pro Leu Pro Leu Pro Ser Glu Phe Leu Pro Ser Phe Pro Leu  
                   20                  25                  30

Val Pro Glu Ser Ser Ser Ala Ala Ser Ser Gly Glu Leu Leu Ser Ser  
           35                  40                  45

Leu Pro Pro Thr Ser Asn Ala Pro Ser Asp Pro Ala Thr Thr Thr Ala  
       50                  55                  60

Lys Ala Asp Ala Ala Ser Ser Leu Thr Val Asp Val Thr Pro Pro Thr  
       65                  70                  75                  80

Ala Lys Ala Pro Thr Thr Val Glu Asp Arg Val Gly Asp Ser Thr Pro  
                   85                  90                  95

Val Ser Glu Lys Pro Val Ser Ala Ala Val Asp Ala Asn  
           100                  105

&lt;210&gt; 695

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 695

Ala Trp Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr  
       1                  5                  10                  15

Leu His Arg Ile Pro Thr  
           20

&lt;210&gt; 696

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 696

Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro  
       1                  5                  10

&lt;210&gt; 697

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 697

Trp Gly Gly Gln Gly Leu Leu Gly  
       1                  5

&lt;210&gt; 698

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

396

&lt;400&gt; 698

Arg Asn Gly Ala Leu Leu Asp Lys Asn Phe Phe Asn Ala Asn Ser His  
 1 5 10 15

Phe Pro Val Lys Gly Glu Arg Ile Arg Arg  
 20 25

&lt;210&gt; 699

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (83)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 699

Arg Gly Ser Gly Phe Gly Trp Thr Ser Phe Pro Arg Pro Leu Pro Thr  
 1 5 10 15

Glu Leu Thr Cys Pro Gly Phe His Arg Glu Arg Ala Phe Pro Pro Asp  
 20 25 30

Gly Arg Val Arg Gly Val Arg Gly Trp Gly Ile Arg Arg Gly Cys Arg  
 35 40 45

Ala Val Trp Gly Val Gly Ala Cys Gly Cys Ser Pro Gly Ser Ser Trp  
 50 55 60

Arg Gly Ser Ala His Arg Ala Ser Gly Pro Ala Asp Leu Pro Val Ala  
 65 70 75 80

Cys Arg Xaa Glu Gly Gly Ala Asp Ser Pro Ser Leu Leu Pro Ser Pro  
 85 90 95

Pro

&lt;210&gt; 700

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 700

Ala Val Trp Gly Val Gly Ala Cys Gly Cys Ser Pro Gly Ser Ser Trp  
 1 5 10 15

Arg Gly Ser Ala His Arg Ala  
 20

&lt;210&gt; 701

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

397

&lt;400&gt; 701

Tyr Arg Pro Thr Met Glu Lys Met Lys Gln Val Val Thr Gln Thr Arg  
1 5 10 15

Trp Met Arg Pro Asp Ala Lys Arg Ala Asn Arg Arg His Arg Arg Ile  
20 25 30

Ser Gly Lys Ile Phe Ala Trp Asn Pro Leu Pro Lys Thr Arg Phe Ser  
35 40 45

Arg Leu Leu Lys Ala Val Ser Glu Asn Thr Lys Arg Pro Glu Pro Ser  
50 55 60

Arg Pro Pro Trp Met Val Ser His Ser Val Glu Ala Ser  
65 70 75

&lt;210&gt; 702

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 702

Phe Ala Trp Asn Pro Leu Pro Lys Thr Arg Phe Ser Arg Leu Leu Lys  
1 5 10 15

Ala Val Ser Glu Asn Thr Lys Arg Pro Glu Pro  
20 25

&lt;210&gt; 703

&lt;211&gt; 93

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (28)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

<222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (33)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (35)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 703  
 Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val Ser  
 1 5 10 15  
 Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa  
 20 25 30  
 Xaa Xaa Xaa Xaa Xaa Xaa Trp Ile Phe Gly Val Leu His Val Val His  
 35 40 45  
 Ala Ser Val Val Thr Ala Tyr Leu Phe Thr Val Ser Asn Ala Phe Gln  
 50 55 60  
 Gly Met Phe Ile Phe Leu Phe Leu Cys Val Leu Ser Arg Lys Ile Gln  
 65 70 75 80  
 Glu Glu Tyr Tyr Arg Leu Phe Lys Asn Val Pro Cys Cys  
 85 90

399

<210> 704  
<211> 55  
<212> PRT  
<213> Homo sapiens

<400> 704  
Trp Ile Phe Gly Val Leu His Val Val His Ala Ser Val Val Thr Ala  
1 5 10 15  
Tyr Leu Phe Thr Val Ser Asn Ala Phe Gln Gly Met Phe Ile Phe Leu  
20 25 30  
Phe Leu Cys Val Leu Ser Arg Lys Ile Gln Glu Glu Tyr Tyr Arg Leu  
35 40 45  
Phe Lys Asn Val Pro Cys Cys  
50 55

<210> 705  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 705  
Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val Ser  
1 5 10 15  
Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg  
20 25

<210> 706  
<211> 66  
<212> PRT  
<213> Homo sapiens

<400> 706  
Ile Ile Tyr Lys Val Phe Arg His Thr Ala Gly Leu Lys Pro Glu Val  
1 5 10 15  
Ser Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Gly Ala Leu Ala Leu  
20 25 30  
Leu Phe Leu Leu Gly Thr Thr Trp Ile Phe Gly Val Leu His Val Val  
35 40 45  
His Ala Ser Val Val Thr Ala Tyr Leu Phe Thr Val Ser Asn Ala Phe  
50 55 60  
Gln Gly  
65

<210> 707  
<211> 32  
<212> PRT  
<213> Homo sapiens

400

&lt;400&gt; 707

Glu Val Ser Cys Phe Glu Asn Ile Arg Ser Cys Ala Arg Gly Ala Leu  
 1 5 10 15

Ala Leu Leu Phe Leu Leu Gly Thr Thr Trp Ile Phe Gly Val Leu His  
 20 25 30

&lt;210&gt; 708

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 708

Thr Thr Ile Leu Arg Thr Cys Thr Ile Val Cys Phe Tyr Tyr Trp Phe  
 1 5 10 15

Asn Gly Val Met Val Leu Leu Phe Phe Leu Asp Arg Asn Leu Leu Thr  
 20 25 30

Phe Asn Gln Ala Ser Ile Met Pro Phe Ser Asn Thr Asp Phe Leu His  
 35 40 45

Cys Leu Ser Phe Lys Lys Lys Leu Met Leu Leu Arg Tyr Ile Phe Tyr  
 50 55 60

Val Val Leu Thr Gly Pro Thr Leu Ser Leu Lys Gly Asp Glu Asn Gln  
 65 70 75 80

Ile Lys Asn Leu Phe Thr  
 85

&lt;210&gt; 709

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 709

Ile Val Cys Phe Tyr Tyr Trp Phe Asn Gly Val Met Val Leu Leu Phe  
 1 5 10 15

Phe Leu Asp Arg Asn Leu Leu  
 20

&lt;210&gt; 710

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 710

Leu Leu Arg Tyr Ile Phe Tyr Val Val Leu Thr Gly Pro Thr Leu Ser  
 1 5 10 15

401

Leu Lys Gly Asp Glu Asn Gln Ile  
20

&lt;210&gt; 711

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 711

Ala Leu Thr Arg Ile Pro Pro Gly Asp Trp Val Ile Asn Val Thr Ala  
1 5 10 15

Val Ser Phe Ala Gly Lys Thr Thr Ala Arg Phe Phe Xaa His Ser Ser  
20 25 30

Pro Pro Ser Leu Gly Asp Gln Ala Arg Thr Asp Pro Gly His Gln Arg  
35 40 45

Arg Asp  
50

&lt;210&gt; 712

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 712

Ser Met Leu Leu Leu Phe Pro Leu Gln Glu Arg Pro Gln Gln Asp Ser  
1 5 10 15

Phe Ile Arg Leu Leu Ala Trp Gly Thr Arg Leu Glu Leu Thr Leu  
20 25 30

Asp Ile Lys Gly Gly Ile  
35

&lt;210&gt; 713

&lt;211&gt; 130

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (76)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

402

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (98)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (113)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 713

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Leu | Trp | Ala | Asp | Gly | Phe | Ser | Ser | His | Ile | Ile | Pro | Pro | Leu |
| 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     |     | 15  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Arg | Val | Ser | Ser | Ser | Leu | Val | Pro | Gln | Ala | Arg | Arg | Arg | Arg |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Glu | Ser | Cys | Cys | Gly | Leu | Ser | Cys | Lys | Gly | Asn | Ser | Ser | Asn |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Asp | Tyr | Pro | Val | Thr | Gly | Arg | Asn | Ser | Cys | Glu | Arg | Ala | Pro | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Ala | Phe | Ala | Leu | His | Phe | Gln | Glu | Arg | Thr | Xaa | Ile | Thr | Gly | Xaa |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Glu | Asp | Pro | Gly | Pro | Phe | Gln | Ser | Xaa | Gly | Arg | Val | Thr | Ala | Ser |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Xaa | Thr | Leu | Ala | Cys | Ser | His | Val | Ala | Met | Thr | Pro | Ala | Gly | Cys |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Gln | Ala | Leu | Gly | Thr | Pro | Ser | Ser | Tyr | Cys | Val | Arg | Lys | Ala | Pro |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |
|-----|-----|
| Arg | Ala |
|     | 130 |

&lt;210&gt; 714

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 714

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Ala | Arg | Arg | Arg | Met | Lys | Glu | Ser | Cys | Cys | Gly | Leu | Ser | Cys |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Asn | Ser | Ser | Asn | Ile | Asp | Tyr | Pro | Val | Thr |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |



403

<210> 715  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 715  
Leu Trp Arg Ser Ser Gly Val Glu Arg  
1 5

<210> 716  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 716  
Leu Gln Glu Val Asn Ile Thr Leu Pro Glu Asn Ser Val Trp Tyr Glu  
1 5 10 15  
Arg Tyr Lys Phe Asp Ile Pro Val Phe His Leu  
20 25

<210> 717  
<211> 110  
<212> PRT  
<213> Homo sapiens

<400> 717  
Met Gln Gly Ser Gly Ser Gln Phe Arg Ala Cys Leu Leu Cys Leu Cys  
1 5 10 15  
Phe Ser Cys Pro Cys Ser Pro Gly Gly Pro Arg Trp Asn Ser Arg Gln  
20 25 30  
Gly Gly Arg Arg Phe Pro Lys Thr Cys Arg Ala Ile Ser Gln Asn Leu  
35 40 45  
Val Phe Lys Tyr Lys Thr Phe Cys Pro Val Arg Tyr Met Gln Pro His  
50 55 60  
Arg Ser Ser Leu Cys Leu His Phe Thr Ser Tyr Val Phe Ile Leu Ser  
65 70 75 80  
Thr Trp Gly Ser Leu Arg Thr Tyr Ser Thr Asp Leu Lys Lys Lys Lys  
85 90 95  
Lys Asn Ser Arg Gly Gly Pro Val Pro Ile Arg Pro Lys Ser  
100 105 110

<210> 718  
<211> 99  
<212> DNA  
<213> Homo sapiens

<220>

404

&lt;221&gt; SITE

&lt;222&gt; (24)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 718

tagcatgtag ccagtcgaat aacntataag gacaaagtgg agtccacgcg tgcggccgtc 60

tagactagtg gatcccccggtg ctgcaggatt cggcacgag 99

&lt;210&gt; 719

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 719

Met Gln Gly Ser Gly Ser Gln Phe Arg Ala Cys Leu Leu Cys Leu Cys  
1 5 10 15Phe Ser Cys Pro Cys Ser Pro Gly Gly Pro Arg Trp Asn Ser Arg Gln  
20 25 30Gly Gly Arg Arg Phe Pro Lys Thr Cys Arg Ala Ile Ser Gln Asn Leu  
35 40 45Val Phe Lys  
50

&lt;210&gt; 720

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 720

Pro Val Arg Tyr Met Gln Pro His Arg Ser Ser Leu Cys Leu His Phe  
1 5 10 15Thr Ser Tyr Val Phe Ile Leu Ser Thr Trp Gly Ser Leu Arg Thr Tyr  
20 25 30Ser Thr Asp Leu Lys Lys Lys Lys Lys Asn Ser Arg Gly Gly Pro Val  
35 40 45Pro Ile Arg Pro Lys Ser  
50

&lt;210&gt; 721

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 721

Gly Glu Glu Gln Arg Asp Cys Ser Leu Gly Trp Arg Gly Val Gly Met  
1 5 10 15

405

Arg Ala Thr His Cys Gln Ala Ala Arg Met Phe Val Leu Phe Ser Leu  
                   20                                  25                                  30

Pro Lys Tyr Ala Gly Leu  
                   35

&lt;210&gt; 722

&lt;211&gt; 39

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 722

Thr Ser Gly Ser Pro Gly Cys Arg Ile Arg His Glu Leu Pro Gly Glu  
       1                                  5                                  10                                  15

Glu Gln Arg Asp Cys Ser Leu Gly Trp Arg Gly Val Gly Met Arg Ala  
                   20                                  25                                  30

Thr His Cys Gln Ala Ala Arg  
                   35

&lt;210&gt; 723

&lt;211&gt; 128

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 723

Glu Pro Pro Ile Ala Lys Gln Gln Glu Cys Ser Cys Phe Phe Pro Phe  
       1                                  5                                  10                                  15

Gln Asn Met Gln Gly Ser Gly Ser Gln Phe Arg Ala Cys Leu Leu Cys  
                   20                                  25                                  30

Leu Cys Phe Ser Cys Pro Cys Ser Pro Gly Gly Pro Arg Trp Asn Ser  
                   35                                  40                                  45

Arg Gln Gly Gly Arg Arg Phe Pro Lys Thr Cys Arg Ala Ile Ser Gln  
                   50                                  55                                  60

Asn Leu Val Phe Lys Tyr Lys Thr Phe Cys Pro Val Arg Tyr Met Gln  
       65                                  70                                  75                                  80

Pro His Arg Ser Ser Leu Cys Leu His Phe Thr Ser Tyr Val Phe Ile  
                                   85                                  90                                  95

Leu Ser Thr Trp Gly Ser Leu Arg Thr Tyr Ser Thr Asp Leu Lys Lys  
                   100                                  105                                  110

Lys Lys Lys Asn Ser Arg Gly Gly Pro Val Pro Ile Arg Pro Lys Ser  
                   115                                  120                                  125

&lt;210&gt; 724

406

<211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 724  
 Gln Phe Arg Ala Cys Leu Leu Cys Leu Cys Phe Ser Cys Pro Cys Ser  
   1                  5                  10                  15  
 Pro Gly Gly Pro Arg Trp Asn Ser Arg Gln Gly Gly Arg Arg Phe  
                   20                  25                  30

<210> 725  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 725  
 Asn Gln Phe Thr Ser Cys Ile Leu Phe Cys Asp Gly Gly His Trp Arg  
   1                  5                  10                  15  
 Glu Leu Leu Phe Gln Ser Ile  
                   20

<210> 726  
 <211> 101  
 <212> PRT  
 <213> Homo sapiens

<400> 726  
 Ala Met Ser Ser Lys Leu Leu Asn Leu Leu Ala Leu Leu Gln Tyr Ser  
   1                  5                  10                  15  
 Val His Asp His Cys His Pro Arg Arg Leu Leu Lys Arg Gly Ala Arg  
                   20                  25                  30  
 Ala Thr Leu Arg His Lys Gly Trp Gly Pro Ser Ser Leu Arg Gly Cys  
                   35                  40                  45  
 Glu Ser Phe Gln Ile Val Leu Ile Gly Trp Gly Pro Asp Leu Ala Val  
   50                  55                  60  
 Gly Phe Gly Arg Gly Lys Leu Leu Ser Arg Ser Leu Pro Val Arg His  
   65                  70                  75                  80  
 Gly Gly Val Ser Glu Phe Cys Leu Pro His Arg Asp Val Val Arg Leu  
                   85                  90                  95  
 Glu Lys Val Lys Lys  
                   100

<210> 727  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

407

&lt;400&gt; 727

Gly Pro Ser Ser Leu Arg Gly Cys Glu Ser Phe Gln Ile Val Leu Ile  
 1 5 10 15

Gly Trp Gly Pro Asp Leu Ala Val Gly Phe Gly Arg Gly Lys Leu Leu  
 20 25 30

Ser

&lt;210&gt; 728

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 728

Thr Arg Lys Asn Ile Asp Phe Xaa Glu Thr Glu Lys Tyr Tyr Leu Phe  
 1 5 10 15

Ser Phe Ser Asn Asn Val Ser Phe Lys Asn Phe Trp Leu Lys Tyr Asn  
 20 25 30

&lt;210&gt; 729

&lt;211&gt; 161

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 729

Met Pro Arg Lys Thr Ser Lys Cys Arg Gln Leu Leu Cys Ser Gly Ala  
 1 5 10 15

Ser Arg Asn Ala Asp Thr Ala Ala Arg Gln Ser Thr Cys Ser Ser His  
 20 25 30

Arg Pro Pro Gly Lys Ile Pro Ser Leu Gly Pro Arg Arg Xaa Pro Gly  
 35 40 45

Cys Xaa Ser Val Pro Ser Ser Arg Gly Glu Gln Ser Thr Gly Ser Pro

408

50                      55                      60  
 Ala Ala Pro Arg Cys Gly Arg Arg Asp Ala His Arg Gly Leu Pro Gly  
 65                      70                      75                      80  
 Gly Ala Ala Met Thr Pro Gly Asp Thr Trp Ala Ser Phe Asn Pro Arg  
                     85                      90                      95  
 Ala Gly His Ser Lys Ser Gln Gly Glu Gly Gln Glu Ser Ser Gly Ala  
                     100                      105                      110  
 Ser Arg Gln Asp Arg His Pro Val Ser His Trp Val Glu Arg Gln Arg  
                     115                      120                      125  
 Glu Ala Trp Gly Ala Pro Arg Ser Ser Ser Ala Gly Gly Val Lys Val  
                     130                      135                      140  
 Ala Ala Thr Thr Glu Arg Glu Pro Glu Phe Lys Ile Lys Thr Gly Lys  
 145                      150                      155                      160  
 Ala

&lt;210&gt; 730

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 730

Cys Ser Gly Ala Ser Arg Asn Ala Asp Thr Ala Ala Arg Gln Ser Thr  
 1                      5                      10                      15

Cys Ser Ser His Arg Pro Pro Gly Lys Ile Pro Ser Leu Gly Pro Arg  
                     20                      25                      30

Arg Xaa Pro Gly Cys Xaa Ser Val Pro Ser Ser Arg Gly Glu Gln Ser  
                     35                      40                      45

Thr Gly Ser Pro Ala Ala Pro Arg Cys Gly Arg Arg Asp Ala His Arg  
                     50                      55                      60

Gly Leu Pro Gly Gly Ala Ala Met Thr Pro Gly Asp Thr Trp Ala Ser  
                     65                      70                      75                      80

Phe Asn Pro Arg Ala Gly His Ser  
                     85

409

<210> 731  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 731  
 Gln Gly Glu Gly Gln Glu Ser Ser Gly Ala Ser Arg Gln Asp Arg His  
 1 5 10 15  
 Pro Val Ser His Trp Val Glu Arg Gln Arg Glu Ala Trp Gly Ala Pro  
 20 25 30  
 Arg Ser Ser Ser Ala Gly Gly Val Lys Val Ala Ala Thr Thr Glu Arg  
 35 40 45  
 Glu Pro Glu Phe Lys Ile Lys Thr Gly Lys Ala  
 50 55

<210> 732  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<400> 732  
 Ile Arg His Glu Gly Lys Arg Met Leu Asn Glu Ser Arg Lys Pro Leu  
 1 5 10 15  
 Ser Phe Ala Ser Arg Leu Ser Ser Leu Tyr Phe Lys Leu Gly Phe Pro  
 20 25 30  
 Phe Cys Gly Arg Ser Asn Leu Tyr Ser Thr Cys Thr Ala Ala Pro Gly  
 35 40 45  
 Gly Ser Pro Gly Leu Pro Leu Pro Phe Tyr Pro Val Ala Asp Gly  
 50 55 60

<210> 733  
 <211> 176  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (127)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 733  
 Thr Arg Ala Glu Ser Leu Phe Pro Leu Leu His Ala Phe Pro Val Phe  
 1 5 10 15  
 Ile Leu Asn Ser Gly Ser Leu Ser Val Val Ala Ala Thr Phe Thr Pro  
 20 25 30  
 Pro Ala Leu Leu Leu Leu Gly Ala Pro Gln Ala Ser Leu Cys Leu Ser  
 35 40 45

410

Thr Gln Trp Leu Thr Gly Cys Leu Ser Cys Leu Asp Ala Pro Leu Leu  
 50 55 60  
 Ser Cys Pro Ser Pro Trp Leu Leu Leu Cys Pro Ala Leu Gly Leu Lys  
 65 70 75 80  
 Leu Ala His Val Ser Pro Gly Val Met Ala Ala Pro Pro Gly Arg Pro  
 85 90 95  
 Leu Cys Ala Ser Arg Leu Pro His Leu Gly Ala Ala Gly Glu Pro Val  
 100 105 110  
 Leu Cys Ser Pro Arg Leu Leu Gly Thr Glu Leu Gln Pro Gly Xaa Leu  
 115 120 125  
 Arg Gly Pro Arg Leu Gly Ile Leu Pro Gly Gly Arg Trp Glu Glu Gln  
 130 135 140  
 Val Leu Cys Leu Ala Ala Val Ser Ala Phe Leu Asp Ala Pro Glu His  
 145 150 155 160  
 Arg Ser Cys Arg His Phe Glu Val Phe Leu Gly Met Cys Gln Ile Thr  
 165 170 175

&lt;210&gt; 734

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 734

Pro Ala Leu Gly Leu Lys Leu Ala His Val Ser Pro Gly Val Met Ala  
 1 5 10 15

Ala Pro Pro Gly Arg Pro Leu Cys Ala Ser Arg Leu Pro  
 20 25

&lt;210&gt; 735

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 735

Gly Gly Arg Trp Glu Glu Gln Val Leu Cys Leu Ala Ala Val Ser Ala  
 1 5 10 15

Phe Leu Asp Ala Pro Glu His Arg  
 20

&lt;210&gt; 736

&lt;211&gt; 98

&lt;212&gt; PRT



411

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 736

Ser Trp Pro Met Cys Pro Pro Glu Ser Trp Leu Leu Leu Leu Gly Gly  
 1 5 10 15

Leu Cys Val Arg His Val Phe His Thr Trp Gly Gln Leu Ala Ser Pro  
 20 25 30

Cys Ser Val Pro Leu Gly Cys Leu Ala Gln Ser Cys Ser Leu Gly Xaa  
 35 40 45

Ser Val Asp Pro Asp Trp Gly Phe Cys Gln Gly Gly Asp Gly Arg Ser  
 50 55 60

Arg Cys Phe Ala Trp Arg Leu Cys Leu His Phe Trp Thr Pro Gln Ser  
 65 70 75 80

Thr Glu Val Ala Gly Thr Leu Arg Ser Ser Ser Ala Cys Ala Arg Leu  
 85 90 95

His Glu

&lt;210&gt; 737

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 737

Gly Asp Gly Arg Ser Arg Cys Phe Ala Trp Arg Leu Cys Leu His Phe  
 1 5 10 15

Trp Thr Pro Gln Ser Thr Glu Val Ala Gly Thr Leu Arg  
 20 25

&lt;210&gt; 738

&lt;211&gt; 235

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 738

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro  
 1 5 10 15

Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser  
 20 25 30

Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro  
 35 40 45

412

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln  
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro  
 65 70 75 80

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro  
 85 90 95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly  
 100 105 110

Asn Tyr Val Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr Pro Ile  
 115 120 125

Met Pro Ser Pro Ala Asp Ser Thr Asn Ser Gly Asp Asn Met Tyr Thr  
 130 135 140

Leu Met Asn Ala Val Pro Pro Gly Pro Asn Arg Pro Asn Phe Pro Met  
 145 150 155 160

Gly Pro Gly Ser Asp Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser  
 165 170 175

His His Met Asn Gly Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser  
 180 185 190

Lys Asn Ser Pro Asn Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro  
 195 200 205

Arg Asp Asp Gly Glu Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser  
 210 215 220

Glu Ser Tyr Ser Pro Ser Met Thr Met Ser Val  
 225 230 235

&lt;210&gt; 739

&lt;211&gt; 114

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 739

Met Ser Pro Arg Tyr Pro Gly Gly Pro Arg Pro Pro Leu Arg Ile Pro  
 1 5 10 15

Asn Gln Ala Leu Gly Gly Val Pro Gly Ser Gln Pro Leu Leu Pro Ser  
 20 25 30

Gly Met Asp Pro Thr Arg Gln Gln Gly His Pro Asn Met Gly Gly Pro  
 35 40 45

Met Gln Arg Met Thr Pro Pro Arg Gly Met Val Pro Leu Gly Pro Gln  
 50 55 60

Asn Tyr Gly Gly Ala Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro  
 65 70 75 80

413

Gly Met Pro Gly Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro  
                             85                            90                            95

Asn Pro Thr Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly  
                             100                            105                            110

Asn Tyr

<210> 740

<211> 81

<212> PRT

<213> Homo sapiens

<400> 740

Leu Asn Ala Leu Gly Gly Pro Gly Met Pro Gly Met Asn Met Gly Pro  
       1                            5                            10                            15

Gly Gly Gly Arg Pro Trp Pro Asn Pro Thr Asn Ala Asn Ser Ile Pro  
                             20                            25                            30

Tyr Ser Ser Ala Ser Pro Gly Asn Tyr Val Gly Pro Pro Gly Gly Gly  
                             35                            40                            45

Gly Pro Pro Gly Thr Pro Ile Met Pro Ser Pro Ala Asp Ser Thr Asn  
                             50                            55                            60

Ser Gly Asp Asn Met Tyr Thr Leu Met Asn Ala Val Pro Pro Gly Pro  
       65                            70                            75                            80

Asn

<210> 741

<211> 70

<212> PRT

<213> Homo sapiens

<400> 741

Gly Pro Met Gly Gly Leu Gly Gly Met Glu Ser His His Met Asn Gly  
       1                            5                            10                            15

Ser Leu Gly Ser Gly Asp Met Asp Ser Ile Ser Lys Asn Ser Pro Asn  
                             20                            25                            30

Asn Met Ser Leu Ser Asn Gln Pro Gly Thr Pro Arg Asp Asp Gly Glu  
                             35                            40                            45

Met Gly Gly Asn Phe Leu Asn Pro Phe Gln Ser Glu Ser Tyr Ser Pro  
                             50                            55                            60

Ser Met Thr Met Ser Val  
       65                            70

<210> 742

414

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 742

Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp Tyr

1

5

10

&lt;210&gt; 743

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 743

Arg Arg Glu Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp

1

5

10

15

Tyr Pro Phe

&lt;210&gt; 744

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 744

Thr Ile Thr Leu Phe Gln Ser Ala Trp Cys Phe Phe Ser Lys Tyr Cys

1

5

10

15

Thr Asp Phe Thr

20

&lt;210&gt; 745

&lt;211&gt; 105

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 745

Val Arg Gly Cys Glu Asp Gly Gly Gly Gly Gly Ile Trp Gly Gly Trp

1

5

10

15

Trp Pro Gly Gln Gln Met Ala Pro Pro Trp Leu Ser Cys Pro His Arg

20

25

30

Gln Phe Pro His Phe His Ser Gly Arg Gln Arg Arg Gln Ser Asp Leu

35

40

45

Leu Lys Glu Glu Leu Pro Gln Pro Ser Gly Ala Ala Gly Arg Ala Ser

50

55

60

Gly Asn Lys Pro Tyr Thr Pro Pro Pro Ala Ser Asn Ser Leu Thr Leu

65

70

75

80

Arg Leu Leu Ser Phe Arg Phe Asn Ala Phe Asn Arg Ser His Pro Gln

85

90

95

415

Pro Ser Leu Asn Tyr Lys Asp Arg Gln  
100 105

<210> 746  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 746  
Pro Trp Leu Ser Cys Pro His Arg Gln Phe Pro His Phe His Ser Gly  
1 5 10 15

Arg Gln Arg Arg Gln Ser Asp Leu Leu  
20 25

<210> 747  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 747  
Arg Leu Leu Ser Phe Arg Phe Asn Ala Phe Asn Arg Ser His Pro Gln  
1 5 10 15

Pro Ser Leu Asn  
20

<210> 748  
<211> 56  
<212> PRT  
<213> Homo sapiens

<400> 748  
Arg Asp Ser Ser Leu Trp Ala Ala Ala Leu Ser Phe Arg Gln Gln Cys  
1 5 10 15

Ser Ser Leu Ala Ser Cys Leu Val Ser Met Tyr Ser Arg Pro Gly Arg  
20 25 30

Gln His Arg Ala Lys Ala Gly Ala Gly Ser Gln Thr Glu Gln Cys Trp  
35 40 45

Gly Arg Lys Val Asp Ala Val Val  
50 55

<210> 749  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 749  
Cys Leu Val Ser Met Tyr Ser Arg Pro Gly Arg Gln His Arg Ala Lys  
1 5 10 15

416

Ala Gly Ala Gly Ser Gln Thr Glu Gln Cys Trp  
 20 25

&lt;210&gt; 750

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 750

Pro Glu His Gly Phe Ser Ser Cys Asp Phe Trp Glu Gly Ala Pro Ser  
 1 5 10 15

Ser Gly Pro Lys Glu Gly Gly Arg Ser Pro Pro Gln Leu Ala Cys Val  
 20 25 30

Trp Gly Met Asn Leu Ser Ser Pro Pro Cys Leu Ala Leu Leu Thr Asn  
 35 40 45

Arg Ala Cys Leu Ala Val Asn Trp His Arg Val Thr Leu Phe Pro Gly  
 50 55 60

Ile Gln Val Cys Asn Gln Asn Thr Gly Glu Glu Lys Leu Gln Asp Pro  
 65 70 75 80

Cys Pro His Leu Ser Ser  
 85

&lt;210&gt; 751

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 751

Arg Ser Pro Pro Gln Leu Ala Cys Val Trp Gly Met Asn Leu Ser Ser  
 1 5 10 15

Pro Pro Cys Leu Ala Leu Leu Thr Asn Arg Ala Cys Leu Ala  
 20 25 30

&lt;210&gt; 752

&lt;211&gt; 74

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 752

Cys Glu Arg Asp Ser Glu Thr Ser Ser Ile Ala Met Thr Cys Ile Lys  
 1 5 10 15

His Lys Pro Pro Lys Gln Lys Lys Arg Leu Ser Leu Leu Pro Gly Phe  
 20 25 30

Arg Ser Ala Leu Pro Arg Val Cys Arg Cys His Met Ile Thr Val Gln  
 35 40 45

417

Arg Glu Ala Phe Arg Thr His Thr Gly Cys Ser Thr Ser Val His Leu  
 50 55 60

Pro Ser Arg Gly Gly Phe Leu Pro Asp Phe  
 65 70

&lt;210&gt; 753

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 753

Lys Lys Arg Leu Ser Leu Leu Pro Gly Phe Arg Ser Ala Leu Pro Arg  
 1 5 10 15

Val Cys Arg Cys His Met Ile Thr Val Gln Arg Glu  
 20 25

&lt;210&gt; 754

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 754

Gln Ala Phe Val Leu Leu Ser Asp Leu Leu Leu Ile Phe Ser Pro Gln  
 1 5 10 15

Met Ile Val Gly Gly Arg Asp Phe Leu Arg Pro Leu Val Phe Phe Pro  
 20 25 30

Glu Ala Thr Leu Gln Ser Glu Leu Ala Ser Phe Leu Met Asp His Val  
 35 40 45

Phe Ile Gln Pro Gly Asp Leu Gly Ser Gly Ala  
 50 55

&lt;210&gt; 755

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 755

Ala Cys Ser Tyr Leu Leu Cys Asn Pro Glu Phe Thr Phe Phe Ser Arg  
 1 5 10 15

Ala Asp Phe Ala Arg Ser Gln Leu Val Asp Leu Leu Thr Asp Arg Phe  
 20 25 30

Gln Gln Glu Leu Glu Glu Leu Leu Gln Val Gly  
 35 40

&lt;210&gt; 756

&lt;211&gt; 35

&lt;212&gt; PRT

418

&lt;213&gt; Homo sapiens

&lt;400&gt; 756

Gln Lys Gln Leu Ser Ser Leu Arg Asp Arg Met Val Ala Phe Cys Glu  
 1 5 10 15  
 Leu Cys Gln Ser Cys Leu Ser Asp Val Asp Thr Glu Ile Gln Glu Gln  
 20 25 30  
 Val Ser Thr  
 35

&lt;210&gt; 757

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 757

Gln Val Ile Leu Pro Ala Leu Thr Leu Val Tyr Phe Ser Ile Leu Trp  
 1 5 10 15  
 Thr Leu Thr His Ile Ser Lys Ser Asp Ala Ser  
 20 25

&lt;210&gt; 758

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 758

Ser Thr His Asp Leu Thr Arg Trp Glu Leu Tyr Glu Pro Cys Cys Gln  
 1 5 10 15  
 Leu Leu Gln Lys Ala Val Asp Thr Gly Xaa Val Pro His Gln Val  
 20 25 30

&lt;210&gt; 759

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 759

Thr Ser Phe Leu Phe Pro Leu Gln Ala Phe Val Leu Leu Ser Asp Leu  
 1 5 10 15  
 Leu Leu Ile Phe Ser Pro Gln Met Ile Val Gly Gly Arg Asp Phe Leu  
 20 25 30  
 Arg Pro Leu Val Phe Phe Pro Glu Ala Thr Leu Gln Ser Glu Leu Ala  
 35 40 45



419

Ser Phe Leu Met Asp His Val Phe Ile Gln Pro Gly Asp Leu Gly Ser  
 50 55 60

Gly Ala  
 65

<210> 760  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<400> 760  
 Gly Trp Gly Ala Cys Ser Tyr Leu Leu Cys Asn Pro Glu Phe Thr Phe  
 1 5 10 15

Phe Ser Arg Ala Asp Phe Ala Arg Ser Gln Leu Val Asp Leu Leu Thr  
 20 25 30

Asp Arg Phe Gln Gln Glu Leu Glu Glu Leu Leu Gln Val Gly Ala Gly  
 35 40 45

Ala Gly Gln Trp Asp Thr Pro Asn Lys Gly Gly Arg Gly Cys Lys Thr  
 50 55 60

Gly Asp Val Asp  
 65

<210> 761  
 <211> 78  
 <212> PRT  
 <213> Homo sapiens

<400> 761  
 Val Trp Val Leu Asp Gly Ile Met Gly Thr Glu Glu Ser Val Ser Ser  
 1 5 10 15

Phe Phe Pro Phe Lys Pro Leu Cys Pro Gln Lys Gln Leu Ser Ser Leu  
 20 25 30

Arg Asp Arg Met Val Ala Phe Cys Glu Leu Cys Gln Ser Cys Leu Ser  
 35 40 45

Asp Val Asp Thr Glu Ile Gln Glu Gln Val Ser Thr Asp Ser Ser Gly  
 50 55 60

Ser Asn Lys Ala Ser Ile Pro Ala Pro Ile Pro Arg Arg Asn  
 65 70 75

<210> 762  
 <211> 152  
 <212> PRT  
 <213> Homo sapiens

<220>

420

&lt;221&gt; SITE

&lt;222&gt; (67)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (86)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 762

Asn Ala Ser Leu Pro Ser Thr Ser Glu Trp Leu Ser Ser Ser Ser Pro  
 1 5 10 15

Ser Arg Phe Tyr Trp Cys Leu Trp Ser Trp Phe Pro Leu Phe Phe Ser  
 20 25 30

Ser Ile Thr Phe Pro Phe Leu Pro Gln Ser Thr His Asp Leu Thr Arg  
 35 40 45

Trp Glu Leu Tyr Glu Pro Cys Cys Gln Leu Leu Gln Lys Ala Val Asp  
 50 55 60

Thr Gly Xaa Val Pro His Gln Val Ser Gly Gln Ala Arg Asp Gly Leu  
 65 70 75 80

Gly Ala Gly Gly Leu Xaa Phe Lys Asp Leu Arg Ser Arg Trp Pro Leu  
 85 90 95

Gly Val Ser Ser Leu Ser Ala Trp Ser Gly Gln Ser Glu Glu Asp Gln  
 100 105 110

Val Gly Gly Gly His Leu Leu His Ser Ser Leu Arg Arg Trp Thr Leu  
 115 120 125

Leu Pro Gly Ser Ser Trp Ile Ser Trp Lys Pro Arg Ile Ile Leu Arg  
 130 135 140

Asp Ser Arg Arg Arg Arg Val Asn  
 145 150

&lt;210&gt; 763

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 763

Val Leu Gly Glu Met Leu Leu Trp Ile Phe Phe Pro Ser Gln Ser Ser  
 1 5 10 15

Phe Leu Asp Glu Asp Glu Val Tyr Asn Leu Ala Ala Thr Leu Lys Arg  
 20 25 30

Leu Ser Ala Phe Tyr Lys  
 35

&lt;210&gt; 764

421

<211> 44  
<212> PRT  
<213> Homo sapiens

<400> 764  
Pro Lys Pro His Phe Ser Asn Pro Leu Leu Leu Gln Val Ile Leu Pro  
1 5 10 15  
Ala Leu Thr Leu Val Tyr Phe Ser Ile Leu Trp Thr Leu Thr His Ile  
20 25 30  
Ser Lys Ser Asp Ala Ser Pro Gly Glu Cys Gly Ser  
35 40

<210> 765  
<211> 7  
<212> PRT  
<213> Homo sapiens

<400> 765  
His Cys Gln Phe Leu Leu Gly  
1 5

<210> 766  
<211> 53  
<212> PRT  
<213> Homo sapiens

<400> 766  
Glu Phe Gly Thr Ser Leu Val Ala Leu Glu Leu His Glu Leu Leu Tyr  
1 5 10 15  
His Trp Glu Thr Arg Ala Gln Pro Ser Leu Ile Leu Tyr Val Val Ser  
20 25 30  
Asp Leu Arg Trp Met Glu Phe Arg Thr Ser Cys Leu Leu Phe Asp Phe  
35 40 45  
Val Leu Phe Leu Glu  
50

<210> 767  
<211> 54  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (17)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 767  
Thr Lys Pro Gly Met Val Gly His Val Pro Ile Val Pro Ala Thr Lys  
1 5 10 15

422

Xaa Ala Glu Ala Gly Gly Ser Pro Glu Pro Gly Ser Ser Thr Leu Gln  
                   20                  25                  30  
 Trp Pro Met Ile Thr Pro Cys Thr Pro Ser Trp Ala Thr Glu Pro Asp  
                   35                  40                  45  
 His Val Ser Glu Asp Glu  
                   50

<210> 768  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 768  
 Leu Leu Tyr His Trp Glu Thr Arg Ala Gln Pro Ser Leu Ile Leu Tyr  
   1                  5                  10                  15  
 Val Val Ser Asp Leu Arg Trp Met Glu Phe Arg Thr Ser Cys  
                   20                  25                  30

<210> 769  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 769  
 Leu Ala Val Ser Thr Ser Phe Ile Cys Cys Ala Asp Ile Ser Thr Ala  
   1                  5                  10                  15  
 Leu Pro Leu Gly Ser Ser Arg Pro Ala Pro Ala Pro Arg His Arg Glu  
                   20                  25                  30  
 His Glu His Gly His Gln Ala Arg Pro Pro Arg Leu Leu Xaa Thr Ser  
                   35                  40                  45  
 Leu Met Pro Leu Ser Thr Pro Ala Ala Ala Gln Leu Leu Trp Thr Gln  
                   50                  55                  60  
 Leu Thr Pro Met Gly Gly Arg Pro Gly Gly Arg His Ser Pro Pro Thr  
   65                  70                  75                  80  
 Leu His Thr Gly Pro Arg Ala Leu Pro Pro Gly Pro Pro His Pro Ser  
                   85                  90                  95  
 Leu His Val Ala Ala Leu Ser Leu Leu Arg  
                   100                  105

<210> 770  
 <211> 85

423

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 770

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Ala | Val | Pro | His | Gln | Pro | Pro | Gly | Thr | Glu | Ser | Thr | Ser | Met |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Thr | Lys | Pro | Gly | Leu | Pro | Gly | Cys | Ser | Xaa | Arg | Pro | Leu | Cys | His |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Gln | His | Gln | Leu | Xaa | Pro | Ser | Tyr | Phe | Gly | His | Ser | Ser | Pro | Pro |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Gly | Ala | Val | Leu | Val | Gly | Val | Thr | Pro | His | Pro | Arg | Cys | Thr | Pro |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Gly | Pro | Cys | Arg | Leu | Gly | Leu | His | Thr | His | Pro | Cys | Thr | Trp |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| Gln | Leu | Cys | Leu | Cys |
|     |     |     |     | 85  |

&lt;210&gt; 771

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 771

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Ala | Asp | Ile | Ser | Thr | Ala | Leu | Pro | Leu | Gly | Ser | Ser | Arg | Pro | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ala | Pro | Arg | His | Arg | Glu | His | Glu | His | Gly | His |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |

&lt;210&gt; 772

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 772

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Thr | Gln | Leu | Thr | Pro | Met | Gly | Gly | Arg | Pro | Gly | Gly | Arg | His | Ser |
| 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Thr | Leu | His | Thr | Gly | Pro | Arg |
|     |     |     | 20  |     |     |     | 25  |     |

424

<210> 773  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

<400> 773  
 His Gln Pro Pro Gly Thr Glu Ser Thr Ser Met Gly Thr Lys Pro Gly  
           1                  5                  10                  15  
 Leu Pro Gly Cys  
                   20

<210> 774  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<400> 774  
 Ser Arg Gly Ser Leu Leu Pro Pro His Leu Pro His Arg Val Val Val  
           1                  5                  10                  15  
 Arg Val His Arg Gly Ala Lys Ser Leu Lys Ala Leu Arg Gln Tyr Ile  
                   20                  25                  30  
 Gly Ala Ala His Leu Gln Leu Pro Trp Asp Gly Lys Asp Pro Ala Arg  
           35                  40                  45  
 Pro Leu Gly Ile Thr Leu Cys Leu Gln Met Glu Ile Gln Val Leu Gly  
           50                  55                  60

<210> 775  
 <211> 150  
 <212> PRT  
 <213> Homo sapiens

<400> 775  
 Cys Cys Ser Phe Gly Phe Tyr Tyr Met Val Gly Ser Asp Thr Ala Glu  
           1                  5                  10                  15  
 Lys Gln Gly Pro Ile Pro Gly Ser Gln Thr Gln Glu Gly Pro Trp Leu  
           20                  25                  30  
 Ser Arg His Thr His Ser Pro Arg Ala Val Pro Glu Ser Ser Thr Ala  
           35                  40                  45  
 Pro Ala Gln Pro Leu Leu Leu Pro Leu Pro Ala Pro Gln Ala Arg Arg  
           50                  55                  60  
 Trp Ala Ser Asn Ala Asn Gly Trp Gly Trp Asp His Gln Arg Glu Gly  
           65                  70                  75                  80  
 Gln Ala Asn Tyr Pro Tyr Ser Ala Arg Pro Ala Pro His Asn Leu His

425

85

90

95

Pro Gln Tyr Leu Asn Leu His Leu Gln Thr Gln Cys Tyr Ala Gln Gly  
 100 105 110

Ser Gly Trp Val Leu Pro Ile Pro Gly Gln Leu Lys Val Gly Gly Pro  
 115 120 125

Tyr Ile Leu Pro Glu Gly Leu Gln Gly Leu Cys Ser Ser Val His Pro  
 130 135 140

His Asn Asn Pro Val Arg  
 145 150

&lt;210&gt; 776

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 776

His Arg Gly Ala Lys Ser Leu Lys Ala Leu Arg Gln Tyr Ile Gly Ala  
 1 5 10 15

Ala His Leu Gln Leu Pro Trp Asp Gly  
 20 25

&lt;210&gt; 777

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 777

Pro Ala Pro Gln Ala Arg Arg Trp Ala Ser Asn Ala Asn Gly Trp Gly  
 1 5 10 15

Trp Asp His Gln Arg  
 20

&lt;210&gt; 778

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 778

His Pro Gln Tyr Leu Asn Leu His Leu Gln Thr Gln Cys Tyr Ala Gln  
 1 5 10 15

Gly Ser Gly Trp Val Leu Pro  
 20

&lt;210&gt; 779

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

426

&lt;400&gt; 779

Thr Asn Gly Ile Met Gln Tyr Val Thr Phe Cys Val Trp Leu Ile Leu  
 1 5 10 15  
 Phe Ser Ile Met Phe Leu Arg Phe Ile Gln Ala Val Ala Cys Ile Ser  
 20 25 30  
 Thr Ser Phe Leu Phe Leu Ala Glu Tyr Tyr Ser Ile Ile Trp Ile Tyr  
 35 40 45  
 His Asn Ser Phe Thr Tyr Ser Ser Phe Val Ser Ala Val Trp Leu Leu  
 50 55 60

&lt;210&gt; 780

&lt;211&gt; 123

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 780

Tyr Asn Phe Met Phe Asn Phe Ser Lys Asn Cys Gln Lys Val Phe His  
 1 5 10 15  
 Ser Gly Cys Ile Ile Tyr Ile Pro Thr Gly Asn Val Gln Gly Phe Leu  
 20 25 30  
 Phe Phe His Ile Leu Ala Leu Thr Asn Thr Ser Phe Xaa Xaa Xaa Phe  
 35 40 45  
 Cys Phe Phe Ile Ile Ala Thr Leu Val Asp Val Lys Trp His Leu Ile  
 50 55 60  
 Val Leu Ile Cys Ile Ser Leu Met Thr Asn Asp Ile Ile Leu Phe Leu  
 65 70 75 80  
 Cys Ala Tyr Gly Ser Lys Val Phe Pro Trp Arg Asn Val Pro Ser Ser  
 85 90 95  
 Pro Leu Pro Phe Gln Asn Leu Val Ile Cys Leu Leu Leu Phe Ser Phe



427

100                      105                      110  
 Lys Lys Phe Trp Pro Gly Ala Val Ala His Leu  
       115                      120

<210> 781  
 <211> 91  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (79)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 781  
 Cys Val Thr Gln Ala Arg Val Gln Trp Arg Asp Leu Gly Ser Leu Gln  
   1                          5                          10                          15  
 Pro Pro Pro Pro Gly Phe Lys Arg Phe Ser Cys Leu Ser Leu Leu Ser  
                   20                          25                          30  
 Arg Xaa Asp Tyr Met His Leu Pro Pro Arg Pro Ala Asn Phe Cys Ile  
           35                          40                          45  
 Phe Ser Lys Met Gly Phe His His Val Gly Gln Ala Gly Leu Glu Val  
   50                          55                          60  
 Leu Xaa Ser Ser Asp Leu Pro Ala Leu Ala Ser Gln Ser Ala Xaa Ile  
   65                          70                          75                          80  
 Thr Gly Glu Pro Leu Arg Leu Ala Arg Ile Ser  
                   85                          90

<210> 782  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 782  
 Leu Pro Pro Arg Pro Ala Asn Phe Cys Ile Phe Ser Lys Met Gly Phe  
   1                          5                          10                          15  
 His His Val Gly Gln Ala Gly Leu Glu  
           20                          25

428

&lt;210&gt; 783

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 783

Leu Ile Leu Phe Ser Ile Met Phe Leu Arg Phe Ile Gln Ala Val Ala  
1 5 10 15

Cys Ile Ser Thr Ser Phe Leu Phe  
20

&lt;210&gt; 784

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 784

Ala Leu Val Pro Ser Pro Gln Gln Ile Leu Pro Ser Cys Phe Ser Leu  
1 5 10 15

Met Trp Gln Val Thr Thr Lys Ser Ala Leu Val Phe Phe Lys Cys Ile  
20 25 30

Tyr Ile Pro Phe Leu Ser Ala Pro Ser Leu Pro Arg Leu Glu Asn Cys  
35 40 45

Leu Ile Phe Cys Ser Leu Asp Val Gln Ser Gln Leu Val Phe Leu Ser  
50 55 60

Ser Pro Pro Val Ala Gly Val Leu Phe Phe Phe Leu Leu Ser Pro Leu  
65 70 75 80

Gly Ser Lys Ser Cys Ser Thr Val Glu Xaa  
85 90

&lt;210&gt; 785

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 785

Ala Pro Ser Leu Pro Arg Leu Glu Asn Cys Leu Ile Phe Cys Ser Leu  
1 5 10 15

Asp Val Gln Ser Gln Leu Val Phe Leu Ser  
20 25

&lt;210&gt; 786

429

<211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 786  
 Ser Ser Pro Ser Arg Val Arg Leu Arg His Thr Pro Gly  
           1                  5                  10

<210> 787  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (60)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 787  
 Ser Asn Thr Asn Tyr Cys Phe Met Phe Phe Tyr Phe Pro Val Lys Val  
           1                  5                  10                  15

Leu Val Pro Phe Lys Asn Cys Tyr Ile Leu Ser Leu Leu Ile Leu Pro  
                   20                  25                  30

Cys Cys Ile Cys Gly His Gln Phe Pro Arg Xaa Gln Ala Cys Thr Phe  
           35                  40                  45

Cys Leu His Thr Leu Gly Gly Phe Ser Phe Ser Xaa Leu Phe Leu Val  
           50                  55                  60

Leu Leu Ser Phe Tyr Val Gln Thr Gly Phe Ser Val  
           65                  70                  75

<210> 788  
 <211> 119  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (97)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

430

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 788

Gly Thr Ser Arg His Gly Gln Arg Pro Ile Ala Pro Gly Thr Pro Trp  
 1 5 10 15

Gln Arg Glu Pro Arg Val Glu Val Met Asp Pro Ala Gly Gly Pro Arg  
 20 25 30

Gly Val Leu Pro Arg Pro Cys Arg Xaa Leu Val Leu Leu Asn Pro Arg  
 35 40 45

Gly Gly Lys Gly Lys Ala Leu Gln Leu Phe Arg Ser His Val Gln Pro  
 50 55 60

Leu Leu Ala Glu Ala Glu Ile Ser Phe Thr Leu Met Leu Thr Glu Arg  
 65 70 75 80

Arg Asn His Ala Arg Glu Leu Val Arg Ser Glu Glu Leu Gly Arg Trp  
 85 90 95

Xaa Ala Leu Val Val Met Xaa Gly Asp Gly Leu Met His Glu Val Val  
 100 105 110

Asn Gly Leu His Gly Ala Ala  
 115

&lt;210&gt; 789

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 789

Arg Pro Ile Ala Pro Gly Thr Pro Trp Gln Arg Glu Pro Arg Val Glu  
 1 5 10 15

Val Met Asp Pro Ala Gly Gly Pro  
 20

&lt;210&gt; 790

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 790

Ala Ser Gly Pro Leu Met Gly Xaa Ala Val Leu Lys Ile Phe Glu  
 1 5 10 15

&lt;210&gt; 791

431

<211> 18  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 791  
 Leu Leu Arg Ser Ala Leu Xaa Ser Pro His Leu Pro Thr Pro Val Pro  
           1                  5                  10                  15

Leu Val

<210> 792  
 <211> 69  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (2)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (24)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 792  
 Gln Xaa Arg Asn Leu Ala Gln Glu Ala Phe Lys Trp Ile Pro Gln Asp  
           1                  5                  10                  15

Arg Pro Thr Val Arg Ser Arg Xaa Arg Met Gly Leu Ser Ile Arg Leu  
                   20                  25                  30

Pro Ile Leu Ala Ser Asn Cys Cys Ala Leu Pro Phe Xaa Xaa Pro Thr  
           35                  40                  45

Ser Pro Leu Gln Cys Leu Trp Ser Cys His Cys Ser Phe Gln Ala Asn  
           50                  55                  60

Thr Gly Leu Ala Ser  
           65

432

&lt;210&gt; 793

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 793

Gln Met Thr Gln Glu Pro Pro Thr Ser Val Arg Ala His Gly Ile Ala  
 1 5 10 15

Ala Trp Gly Asn Gly Cys Arg Asp Lys Asn Thr Lys Arg Leu Ile Gln  
 20 25 30

Tyr Trp Pro Glu Ser Cys Ser Gly Met Thr Lys Gly Thr Gly Val Gly  
 35 40 45

Arg Trp Gly Glu Xaa Arg Ala Glu Arg Ser Ser  
 50 55

&lt;210&gt; 794

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 794

His Gly Ile Ala Ala Trp Gly Asn Gly Cys Arg Asp Lys Asn Thr Lys  
 1 5 10 15

Arg Leu Ile Gln Tyr  
 20

&lt;210&gt; 795

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 795

Cys Glu Arg Ser Gly Tyr Thr Arg Met Ala Met Asp Thr  
 1 5 10

&lt;210&gt; 796

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 796

Thr Gly Ser Ile Leu Ala Val Gly Lys Lys Tyr Ser Leu Gly Ser Tyr  
 1 5 10 15

Ser Arg Gly Asp Trp His Met Arg Val Val Gly Leu Arg Gly Leu Gly

433

20                      25                      30  
 Ala Ser Thr Leu Gln Gly Leu Leu Ile Gly Ile Lys Pro Asn Lys Pro  
                     35                      40                      45  
 Gln Gly Arg Gly Lys Leu Gln Gly Arg Ser Ser Arg Lys Asp Thr Val  
                     50                      55                      60  
 Leu Trp Pro Ser Pro Glu His Pro His Met Val Ser Met Ala Ile Leu  
                     65                      70                      75                      80  
 Val Tyr Pro Asp Leu Ser His Tyr Ser Asn Pro His Ser Thr Pro Ala  
                     85                      90                      95  
 Ala Leu Leu Gly Cys Trp Pro Pro Phe Arg Glu Gly Glu Ile Leu Gly  
                     100                      105                      110  
 Leu Gln Arg Pro Gly Gln Trp Pro Glu Glu Arg Cys Asp Arg Pro Trp  
                     115                      120                      125  
 Leu Pro Pro Cys  
                     130

<210> 797  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 797  
 Gly Ser Tyr Ser Arg Gly Asp Trp His Met Arg Val Val Gly Leu Arg  
   1                    5                    10                    15  
 Gly Leu Gly Ala Ser Thr Leu Gln Gly Leu Leu Ile Gly  
                     20                    25

<210> 798  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 798  
 Ser Thr Pro Ala Ala Leu Leu Gly Cys Trp Pro Pro Phe Arg Glu Gly  
   1                    5                    10                    15  
 Glu Ile Leu Gly Leu Gln Arg Pro Gly Gln Trp  
                     20                    25

<210> 799  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 799  
 Thr Met Gly Thr Trp Val Asp Trp Leu Thr Thr Asn Thr Ala His Thr  
   1                    5                    10                    15

434

Pro Ala Ile Ala Ala Ala Ile Cys Ala Glu Asp Phe Pro Gln Arg His  
                   20                  25                  30

Cys Gly Ser Val Glu Arg Ser Pro Asp Gln Ala Cys  
                   35                  40

<210> 800  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 800  
 Thr Asn Thr Ala His Thr Pro Ala Ile Ala Ala Ala Ile Cys Ala Glu  
       1                  5                  10                  15

Asp Phe Pro Gln Arg His Cys  
                   20

<210> 801  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 801  
 Met Ser Pro Glu Thr Lys Gly Lys Gly Arg Ser Phe Pro Leu Lys  
       1                  5                  10                  15

<210> 802  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 802  
 Cys Gln Asn Lys Cys Ser Glu Thr Thr Cys Gly Arg Thr Arg Arg Glu  
       1                  5                  10                  15

Ser Asn Lys Gln Ala Arg Ala Met Ala Phe Ile Phe Lys Gly Lys Asp  
                   20                  25                  30

Leu Pro Phe Pro Phe Val Ser Gly Asp Ile Gln Pro Lys Ser Ser Gly  
           35                  40                  45

Ser Met Ala Pro Asp Gln Gln Gly Leu Cys Tyr Leu Gly Ser Trp Arg  
       50                  55                  60

Ser His Leu Tyr Cys Arg Leu Leu Pro Met Asp Gln Val Ser Pro Ala  
       65                  70                  75                  80

Leu Cys

<210> 803  
 <211> 63



435

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 803

Lys Pro Ser Pro Gly Leu Ala Tyr Cys Ser Leu Ser Trp Ser Phe His  
1 5 10 15

Met Leu Phe Leu Asn Ile Cys Ser Gly Ile Thr Ile Pro Val Ile Leu  
20 25 30

Ser Ser Gly Pro Ser His Leu Ser Thr Leu Ser Leu Ala Val Ser Pro  
35 40 45

Arg Arg Pro Gly Thr Trp Val Lys Ala Cys Ser Cys Trp Cys Pro  
50 55 60

&lt;210&gt; 804

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 804

Asn Lys Gln Ala Arg Ala Met Ala Phe Ile Phe Lys Gly Lys Asp Leu  
1 5 10 15

Pro Phe Pro Phe Val Ser Gly Asp Ile  
20 25

&lt;210&gt; 805

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 805

Tyr Leu Gly Ser Trp Arg Ser His Leu Tyr Cys Arg Leu Leu Pro Met  
1 5 10 15

Asp Gln Val Ser Pro  
20

&lt;210&gt; 806

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 806

Gly Ile Thr Ile Pro Val Ile Leu Ser Ser Gly Pro Ser His Leu Ser  
1 5 10 15

Thr Leu Ser Leu Ala Val Ser Pro Arg  
20 25

&lt;210&gt; 807

&lt;211&gt; 11

436

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 807

Leu Glu Arg Leu Gly Val Gly Arg Gly Leu Glu  
 1 5 10

&lt;210&gt; 808

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 808

Asp Leu Pro Pro Cys Trp Thr Thr Leu Lys Glu His Gln Cys Phe Met  
 1 5 10 15

Gln Tyr Gln Leu Phe Thr Ile Gln Cys Lys Val Val Glu Gln Thr Ile  
 20 25 30

Cys Glu Asp Glu Arg Lys Met Glu Ser Thr Cys Leu Thr Leu Ala Xaa  
 35 40 45

Pro Glu Ser Val Arg Gln Xaa Cys Pro Ala Thr Leu Trp Ser Ser Met  
 50 55 60

Asn Ile Cys

65

&lt;210&gt; 809

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 809

Thr Asn Arg Val Xaa Leu Ser Trp Arg Lys Glu Glu Gln Arg Met Gly  
 1 5 10 15

Arg Thr Glu Thr Gly Ala Lys Asp Lys Gly Arg Asp Phe Leu Glu Arg  
 20 25 30

Gly Ser Arg Gly Trp Gln Leu Tyr Thr Gly Ala Ala Asp Thr Glu Glu

437

35

40

45

Val

&lt;210&gt; 810

&lt;211&gt; 207

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 810

Glu Gln Val Leu Ala Leu Leu Trp Pro Arg Phe Glu Leu Ile Leu Glu  
 1 5 10 15

Met Asn Val Gln Ser Val Arg Ser Thr Asp Pro Gln Arg Leu Gly Gly  
 20 25 30

Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu Phe Ser  
 35 40 45

Ser Ala Leu Val Ser Ile Asn Gln Thr Ile Pro Asn Glu Arg Thr Met  
 50 55 60

Gln Leu Leu Gly Gln Leu Gln Val Glu Val Glu Asn Phe Val Leu Arg  
 65 70 75 80

Val Ala Ala Glu Phe Ser Ser Arg Lys Glu Gln Leu Val Phe Leu Ile  
 85 90 95

Asn Asn Tyr Asp Met Met Leu Gly Val Leu Met Glu Arg Ala Ala Asp  
 100 105 110

Asp Ser Lys Glu Val Glu Ser Phe Gln Gln Leu Leu Asn Ala Arg Thr  
 115 120 125

Gln Glu Phe Ile Glu Glu Leu Ser Pro Pro Phe Gly Gly Leu Val  
 130 135 140

Ala Phe Val Lys Glu Ala Glu Ala Leu Ile Glu Arg Gly Gln Ala Glu  
 145 150 155 160

Arg Leu Arg Gly Glu Glu Ala Arg Val Thr Gln Leu Ile Arg Gly Phe  
 165 170 175

Gly Ser Ser Trp Lys Ser Ser Val Glu Ser Leu Ser Gln Asp Val Met  
 180 185 190

Arg Ser Phe Thr Asn Phe Arg Asn Gly Thr Ser Ile Ile Gln Gly  
 195 200 205

&lt;210&gt; 811

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

438

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 811

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Leu | Leu | Lys | Tyr | Arg | Phe | Phe | Tyr | Gln | Phe | Leu | Leu | Gly | Asn | Glu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | Thr | Ala | Lys | Glu | Ile | Arg | Asp | Glu | Tyr | Val | Glu | Thr | Leu | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ile | Tyr | Leu | Ser | Tyr | Tyr | Arg | Ser | Tyr | Leu | Gly | Arg | Leu | Met | Lys |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Tyr | Glu | Glu | Val | Ala | Glu | Lys | Asp | Asp | Leu | Met | Gly | Val | Glu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Thr | Ala | Lys | Lys | Gly | Phe | Xaa | Ser | Lys | Pro | Ser | Leu | Arg | Ser | Arg |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Thr | Ile | Phe | Thr | Leu | Gly | Thr | Arg | Gly | Ser | Val | Ile | Ser | Pro | Thr |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Glu | Ala | Pro | Ile | Leu | Val | Pro | His | Thr | Ala | Gln | Arg |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |

&lt;210&gt; 812

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 812

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gln | Arg | Tyr | Pro | Phe | Glu | Ala | Leu | Phe | Arg | Ser | Gln | His | Tyr | Xaa |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Asp | Asn | Ser | Cys | Arg | Glu | Tyr | Leu | Phe | Ile | Cys | Glu | Phe | Phe |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Ser | Gly | Pro | Xaa | Ala | His | Asp | Leu | Phe | His | Ala | Val | Met | Gly |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Thr | Leu | Ser | Met | Thr | Leu | Lys | His | Leu | Asp | Ser | Tyr | Leu | Ala | Asp |
|     | 50  |     |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Tyr | Asp | Ala | Ile | Ala | Val | Phe | Leu | Cys | Ile | His | Ile | Val | Leu | Arg |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

439

Phe Arg Asn Ile Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr  
85 90 95

Trp

<210> 813  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 813  
Gly Gly Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu  
1 5 10 15

Phe Ser Ser Ala Leu Val Ser Ile Asn Gln  
20 25

<210> 814  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 814  
Ser Arg Lys Glu Gln Leu Val Phe Leu Ile Asn Asn Tyr Asp Met Met  
1 5 10 15

Leu Gly Val Leu  
20

<210> 815  
<211> 411  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (72)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (111)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (127)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (149)  
<223> Xaa equals any of the naturally occurring L-amino acids

440

&lt;400&gt; 815

Ala Leu Leu Lys Tyr Arg Phe Phe Tyr Gln Phe Leu Leu Gly Asn Glu  
 1 5 10 15

Arg Ala Thr Ala Lys Glu Ile Arg Asp Glu Tyr Val Glu Thr Leu Ser  
 20 25 30

Lys Ile Tyr Leu Ser Tyr Tyr Arg Ser Tyr Leu Gly Arg Leu Met Lys  
 35 40 45

Val Gln Tyr Glu Glu Val Ala Glu Lys Asp Asp Leu Met Gly Val Glu  
 50 55 60

Asp Thr Ala Lys Lys Gly Phe Xaa Ser Lys Pro Ser Leu Arg Ser Arg  
 65 70 75 80

Asn Thr Ile Phe Thr Leu Gly Thr Arg Gly Ser Val Ile Ser Pro Thr  
 85 90 95

Glu Leu Glu Ala Pro Ile Leu Val Pro His Thr Ala Gln Arg Xaa Glu  
 100 105 110

Gln Arg Tyr Pro Phe Glu Ala Leu Phe Arg Ser Gln His Tyr Xaa Leu  
 115 120 125

Leu Asp Asn Ser Cys Arg Glu Tyr Leu Phe Ile Cys Glu Phe Phe Val  
 130 135 140

Val Ser Gly Pro Xaa Ala His Asp Leu Phe His Ala Val Met Gly Arg  
 145 150 155 160

Thr Leu Ser Met Thr Leu Lys His Leu Asp Ser Tyr Leu Ala Asp Cys  
 165 170 175

Tyr Asp Ala Ile Ala Val Phe Leu Cys Ile His Ile Val Leu Arg Phe  
 180 185 190

Arg Asn Ile Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr Trp  
 195 200 205

Glu Gln Val Leu Ala Leu Leu Trp Pro Arg Phe Glu Leu Ile Leu Glu  
 210 215 220

Met Asn Val Gln Ser Val Arg Ser Thr Asp Pro Gln Arg Leu Gly Gly  
 225 230 235 240

Leu Asp Thr Arg Pro His Tyr Ile Thr Arg Arg Tyr Ala Glu Phe Ser  
 245 250 255

Ser Ala Leu Val Ser Ile Asn Gln Thr Ile Pro Asn Glu Arg Thr Met  
 260 265 270

Gln Leu Leu Gly Gln Leu Gln Val Glu Val Glu Asn Phe Val Leu Arg  
 275 280 285

Val Ala Ala Glu Phe Ser Ser Arg Lys Glu Gln Leu Val Phe Leu Ile  
 290 295 300

441

Asn Asn Tyr Asp Met Met Leu Gly Val Leu Met Glu Arg Ala Ala Asp  
 305 310 315 320  
 Asp Ser Lys Glu Val Glu Ser Phe Gln Gln Leu Leu Asn Ala Arg Thr  
 325 330 335  
 Gln Glu Phe Ile Glu Glu Leu Leu Ser Pro Pro Phe Gly Gly Leu Val  
 340 345 350  
 Ala Phe Val Lys Glu Ala Glu Ala Leu Ile Glu Arg Gly Gln Ala Glu  
 355 360 365  
 Arg Leu Arg Gly Glu Glu Ala Arg Val Thr Gln Leu Ile Arg Gly Phe  
 370 375 380  
 Gly Ser Ser Trp Lys Ser Ser Val Glu Ser Leu Ser Gln Asp Val Met  
 385 390 395 400  
 Arg Ser Phe Thr Asn Phe Arg Asn Gly Thr Ser  
 405 410

<210> 816  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 816  
 Pro Ala Asp Leu Arg Ala Val Ser Gly Thr Ser Glu Val Gly Leu Met  
 1 5 10 15  
 Leu Leu Glu Leu His His Lys Val Val Asn Val Asp Glu Leu Ser Pro  
 20 25 30  
 Gly Arg Glu Gly Ser Glu Leu Arg Leu Gly Gln His Pro Val Glu Ala  
 35 40 45  
 Met Ile Glu Leu Asp Gln Leu Gly Gln Arg Ser Leu Asn Asp Thr Gly  
 50 55 60  
 Ala Ile Ser Glu Val Gly Glu Thr Pro His Tyr Ile Leu Thr Gln Arg  
 65 70 75 80  
 Phe His

<210> 817  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (12)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>

442

&lt;221&gt; SITE

&lt;222&gt; (28)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 817

Gly Pro His Pro Gly Ala Ser His Ser Ala Ala Xaa Glu Gln Arg Tyr  
 1 5 10 15

Pro Phe Glu Ala Leu Phe Arg Ser Gln His Tyr Xaa Leu Leu Asp Asn  
 20 25 30

Ser Cys Arg Glu Tyr Leu Phe Ile Cys Glu Phe Phe Val Val Ser Gly  
 35 40 45

Pro Xaa Ala His Asp Leu Phe His Ala Val Met Gly Arg Thr Leu Ser  
 50 55 60

Met Thr Leu Lys His Leu Asp Ser Tyr Leu Ala Asp Cys Tyr Asp Ala  
 65 70 75 80

Ile Ala Val Phe Leu Cys Ile His Ile Val Leu Arg Phe Arg Asn Ile  
 85 90 95

Ala Ala Lys Arg Asp Val Pro Ala Leu Asp Arg Tyr Trp Gly Thr Gly  
 100 105 110

Ala Cys Leu Ala Met Ala Thr Val  
 115 120

&lt;210&gt; 818

&lt;211&gt; 303

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 818

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu  
 1 5 10 15

Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn Thr Ser Asp Asp Pro Trp  
 20 25 30

Leu Thr Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe  
 35 40 45

Leu Asp Gln Val Ala Lys Phe Ile Ile Asp Asn Thr Lys Gly Gln Met  
 50 55 60

Leu Gly Leu Gly Asn Pro Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly  
 65 70 75 80

Arg Tyr Val Pro Gly Ser Ser Gly Ser Ser Asn Thr Leu Pro Thr Ala  
 85 90 95



443

Asp Pro Phe Thr Gly Ala Gly Arg Tyr Val Pro Gly Ser Ala Ser Met  
                   100                  105                  110  
 Gly Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr  
                   115                  120                  125  
 Arg Ser Ala Ala Ser Lys Thr Met Asn Ile Tyr Phe Pro Lys Lys Glu  
                   130                  135                  140  
 Ala Val Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu  
                   145                  150                  155                  160  
 Lys Glu Leu Asn Gly Thr Ala Pro Glu Glu Lys Lys Leu Thr Glu Asp  
                   165                  170                  175  
 Asp Leu Ile Leu Leu Glu Lys Ile Leu Ser Leu Ile Cys Asn Ser Ser  
                   180                  185                  190  
 Ser Glu Lys Pro Thr Val Gln Gln Leu Gln Ile Leu Trp Lys Ala Ile  
                   195                  200                  205  
 Asn Cys Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu  
                   210                  215                  220  
 Ser Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu  
                   225                  230                  235                  240  
 Gly Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly  
                   245                  250                  255  
 Lys Pro Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe  
                   260                  265                  270  
 Val Gly Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu  
                   275                  280                  285  
 Met Ser His Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile  
                   290                  295                  300

&lt;210&gt; 819

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 819

His Ile Ala Leu Ala Thr Leu Ala Leu Asn Tyr Ser Val Cys Phe His  
           1                  5                  10                  15

Lys Asp

&lt;210&gt; 820

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

444

&lt;400&gt; 820

His Asn Ile Glu Gly Lys Ala Gln Cys Leu Ser Leu Ile Ser Thr Ile  
 1 5 10 15

Leu Glu Val Val Gln Asp Leu Glu Ala Thr Phe Arg Leu Leu Val Ala  
 20 25 30

Leu Gly Thr Leu Ile Ser Asp Asp Ser Asn Ala Val Gln Leu Ala Lys  
 35 40 45

Ser

&lt;210&gt; 821

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 821

Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr Ser Ser Val Ser Glu Pro  
 1 5 10 15

Ala Lys Val Ser Glu Cys Cys Arg Phe Ile Leu Asn Leu Leu  
 20 25 30

&lt;210&gt; 822

&lt;211&gt; 400

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 822

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu  
 1 5 10 15

Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn Thr Ser Asp Asp Pro Trp  
 20 25 30

Leu Thr Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe  
 35 40 45

Leu Asp Gln Val Ala Lys Phe Ile Ile Asp Asn Thr Lys Gly Gln Met  
 50 55 60

Leu Gly Leu Gly Asn Pro Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly  
 65 70 75 80

Arg Tyr Val Pro Gly Ser Ser Gly Ser Ser Asn Thr Leu Pro Thr Ala  
 85 90 95

Asp Pro Phe Thr Gly Ala Gly Arg Tyr Val Pro Gly Ser Ala Ser Met  
 100 105 110

Gly Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr  
 115 120 125

445

Arg Ser Ala Ala Ser Lys Thr Met Asn Ile Tyr Phe Pro Lys Lys Glu  
 130 135 140  
 Ala Val Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu  
 145 150 155 160  
 Lys Glu Leu Asn Gly Thr Ala Pro Glu Glu Lys Lys Leu Thr Glu Asp  
 165 170 175  
 Asp Leu Ile Leu Leu Glu Lys Ile Leu Ser Leu Ile Cys Asn Ser Ser  
 180 185 190  
 Ser Glu Lys Pro Thr Val Gln Gln Leu Gln Ile Leu Trp Lys Ala Ile  
 195 200 205  
 Asn Cys Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu  
 210 215 220  
 Ser Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu  
 225 230 235 240  
 Gly Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly  
 245 250 255  
 Lys Pro Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe  
 260 265 270  
 Val Gly Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu  
 275 280 285  
 Met Ser His Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile His  
 290 295 300  
 Ile Ala Leu Ala Thr Leu Ala Leu Asn Tyr Ser Val Cys Phe His Lys  
 305 310 315 320  
 Asp His Asn Ile Glu Gly Lys Ala Gln Cys Leu Ser Leu Ile Ser Thr  
 325 330 335  
 Ile Leu Glu Val Val Gln Asp Leu Glu Ala Thr Phe Arg Leu Leu Val  
 340 345 350  
 Ala Leu Gly Thr Leu Ile Ser Asp Asp Ser Asn Ala Val Gln Leu Ala  
 355 360 365  
 Lys Ser Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr Ser Ser Val Ser  
 370 375 380  
 Glu Pro Ala Lys Val Ser Glu Cys Cys Arg Phe Ile Leu Asn Leu Leu  
 385 390 395 400

&lt;210&gt; 823

&lt;211&gt; 29

&lt;212&gt; PRT

446

&lt;213&gt; Homo sapiens

&lt;400&gt; 823

Leu Asn Leu Leu Leu Ile Thr Gln Lys Val Lys Cys Trp Asp Leu Gly  
1 5 10 15

Ile Pro Ala Phe Gln Ile His Leu Gln Val Val Val Gly  
20 25

&lt;210&gt; 824

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 824

Ile Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu Gly  
1 5 10 15

Ala Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro  
20 25

&lt;210&gt; 825

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 825

Ala Ile Glu Leu Lys Ser Gly Ser Asn Lys Asn Ile His Ile Ala Leu  
1 5 10 15

Ala Thr Leu Ala Leu Asn  
20

&lt;210&gt; 826

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 826

Val Gln Leu Ala Lys Ser Leu Gly Val Asp Ser Gln Ile Lys Lys Tyr  
1 5 10 15

Ser Ser Val Ser Glu Pro Ala  
20

&lt;210&gt; 827

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 827

Tyr Glu Gly Lys Glu Phe Asp Tyr Val Phe Ser Ile Asp Val Asn Glu  
1 5 10 15

447

Gly Gly Pro Ser Tyr Lys Leu Pro Tyr Asn  
20 25

<210> 828  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 828  
Ala Tyr Asn Phe Leu Gln Lys Asn Asp Leu Asn Pro Met Phe Leu Asp  
1 5 10 15

Gln Val Ala Lys Phe Ile Ile Asp Asn Thr  
20 25

<210> 829  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 829  
Ser Phe Ser Asp Pro Phe Thr Gly Gly Gly Arg Tyr Val Pro Gly  
1 5 10 15

<210> 830  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 830  
Thr Ala Asp Pro Phe Thr Gly Ala Gly Arg Tyr  
1 5 10

<210> 831  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 831  
Thr Thr Met Ala Gly Val Asp Pro Phe Thr Gly Asn Ser Ala Tyr Arg  
1 5 10 15

Ser Ala Ala

<210> 832  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 832  
Asn Ile Tyr Phe Pro Lys Lys Glu Ala  
1 5

448

<210> 833  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 833  
Thr Phe Asp Gln Ala Asn Pro Thr Gln Ile Leu Gly Lys Leu Lys Glu  
1 5 10 15

Leu Asn Gly

<210> 834  
<211> 30  
<212> PRT  
<213> Homo sapiens

<400> 834  
Pro Glu Asp Ile Val Phe Pro Ala Leu Asp Ile Leu Arg Leu Ser Ile  
1 5 10 15

Lys His Pro Ser Val Asn Glu Asn Phe Cys Asn Glu Lys Glu  
20 25 30

<210> 835  
<211> 31  
<212> PRT  
<213> Homo sapiens

<400> 835  
Gln Phe Ser Ser His Leu Ile Asn Leu Leu Asn Pro Lys Gly Lys Pro  
1 5 10 15

Ala Asn Gln Leu Leu Ala Leu Arg Thr Phe Cys Asn Cys Phe Val  
20 25 30

<210> 836  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 836  
Gln Ala Gly Gln Lys Leu Met Met Ser Gln Arg Glu Ser Leu Met Ser  
1 5 10 15

His Ala Ile Glu Leu Lys Ser Gly Ser Asn  
20 25

<210> 837  
<211> 139  
<212> PRT  
<213> Homo sapiens

449

&lt;400&gt; 837

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Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu His Glu
 1              5              10              15

His Ile Gln Arg Leu Ser Lys Val Val Thr Ala Asn His Arg Ala Leu
          20              25              30

Gln Ile Pro Glu Val Tyr Leu Arg Glu Ala Pro Trp Pro Ser Ala Gln
          35              40              45

Ser Glu Ile Arg Thr Ile Ser Ala Tyr Lys Thr Pro Arg Asp Lys Val
          50              55              60

Gln Cys Ile Leu Arg Met Cys Ser Thr Ile Met Asn Leu Leu Ser Leu
          65              70              75              80

Ala Asn Glu Asp Ser Val Pro Gly Ala Asp Asp Phe Val Pro Val Leu
          85              90              95

Val Phe Val Leu Ile Lys Ala Asn Pro Pro Cys Leu Leu Ser Thr Val
          100              105              110

Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys Leu Ser Gly Glu Glu Ser
          115              120              125

Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu
          130              135

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&lt;210&gt; 838

&lt;211&gt; 144

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 838

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Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu His Glu
 1              5              10              15

His Ile Gln Arg Leu Ser Lys Val Val Thr Ala Asn His Arg Ala Leu
          20              25              30

Gln Ile Pro Glu Val Tyr Leu Arg Glu Ala Pro Trp Pro Ser Ala Gln
          35              40              45

Ser Glu Ile Arg Thr Ile Ser Ala Tyr Lys Thr Pro Arg Asp Lys Val
          50              55              60

Gln Cys Ile Leu Arg Met Cys Ser Thr Ile Met Asn Leu Leu Ser Leu
          65              70              75              80

Ala Asn Glu Asp Ser Val Pro Gly Ala Asp Asp Phe Val Pro Val Leu
          85              90              95

Val Phe Val Leu Ile Lys Ala Asn Pro Pro Cys Leu Leu Ser Thr Val
          100              105              110

Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys Leu Ser Gly Glu Glu Ser

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450

115

120

125

Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu Phe Ile Lys Thr Ile  
 130 135 140

&lt;210&gt; 839

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 839

Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu  
 1 5 10

&lt;210&gt; 840

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 840

Glu Ala Pro Trp Pro Ser Ala Gln Ser Glu Ile  
 1 5 10

&lt;210&gt; 841

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 841

Ser Gly Glu Glu Ser Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu  
 1 5 10 15

Phe Ile Lys Thr Ile  
 20

&lt;210&gt; 842

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 842

Ala Asp Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn  
 1 5 10 15

Pro Pro

&lt;210&gt; 843

&lt;211&gt; 12

&lt;212&gt; PRT



451

&lt;213&gt; Homo sapiens

&lt;400&gt; 843

Tyr Lys Thr Pro Arg Asp Lys Val Gln Cys Ile Leu  
1 5 10

&lt;210&gt; 844

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 844

Gly Ala Asp Asp Phe Val Pro Val Leu Val Phe Val Leu Ile Lys  
1 5 10 15

&lt;210&gt; 845

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 845

Pro Val Leu Val Phe Val Leu Ile Lys Ala Asn Pro  
1 5 10

&lt;210&gt; 846

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 846

Ser Ala Arg Ala Ser Thr Gln Pro Pro Ala Gly Gln His Pro Gly Pro  
1 5 10 15

Cys

&lt;210&gt; 847

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 847

Met Pro Gly Arg Trp Arg Trp Gln Arg Asp Met His Pro Ala Arg Lys  
1 5 10 15

Leu Leu Ser Leu Leu Phe Leu Ile Leu Met Gly Thr Glu Leu Thr Gln  
20 25 30

Asp

&lt;210&gt; 848

&lt;211&gt; 19

452

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 848

Ser Ala Ala Pro Asp Ser Leu Leu Arg Ser Ser Lys Gly Ser Thr Arg  
1 5 10 15

Gly Ser Leu

&lt;210&gt; 849

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 849

Ala Ala Ile Val Ile Trp Arg Gly Lys Ser Glu Ser Arg Ile Ala Lys  
1 5 10 15

Thr Pro Gly Ile  
20

&lt;210&gt; 850

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 850

Pro Leu Gly Ile Thr Leu Pro Leu Gly Ala Pro Glu Thr Gly Gly Gly  
1 5 10 15

Asp

&lt;210&gt; 851

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 851

Cys Ala Ala Glu Thr Trp Lys Gly Ser Gln Arg Ala Gly Gln Leu Cys  
1 5 10 15

Ala Leu Leu Ala  
20

&lt;210&gt; 852

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 852

Phe Arg Gly Gly Gly Thr Leu Val Leu Pro Pro Thr His Thr Pro Glu  
1 5 10 15

453

Trp Leu Ile Leu  
20

<210> 853  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 853  
Asn Ser Ala Arg Ala Ser Thr Gln Pro Pro Ala Gly Gln His Pro Gly  
1 5 10 15

Pro Cys Met Pro Gly Arg Trp Arg Trp Gln Arg Asp  
20 25

<210> 854  
<211> 80  
<212> PRT  
<213> Homo sapiens

<400> 854  
Tyr Ile Val Gln Gly Thr Thr Ser Pro Phe Glu Met Pro Thr Ile Pro  
1 5 10 15

Thr Pro Ala Arg His Arg Ala Pro His Ser Pro Pro Ala Gly His Val  
20 25 30

Ala Thr Ala Pro Gln Ala Leu His Ile Lys Pro Ala Met His Thr Ala  
35 40 45

Gly Arg His Ala Gly Cys Pro Ser Arg Ser Gln Arg His Asn Pro His  
50 55 60

Arg Leu Phe Leu Glu Pro Pro Arg Ala Ala Leu Cys Pro Lys Gly Gly  
65 70 75 80

<210> 855  
<211> 97  
<212> PRT  
<213> Homo sapiens

<400> 855  
Ala Ser Asn Ala His Ser Trp Pro Ala Arg Trp Leu Pro Phe Gln Val  
1 5 10 15

Ser Ala Ala Gln Ser Pro Pro Pro Val Ser Gly Ala Pro Lys Gly Ser  
20 25 30

Val Met Pro Lys Gly Arg Met Ser His Ser Gly Val Cys Val Gly Gly  
35 40 45

454

Arg Thr Lys Val Pro Pro Pro Leu Lys Met Pro Gly Val Leu Ala Ile  
 50 55 60

Arg Leu Ser Leu Phe Pro Leu Gln Met Thr Ile Ala Ala Lys Asp Pro  
 65 70 75 80

Leu Val Leu Pro Phe Glu Leu Leu Ser Arg Glu Ser Gly Ala Ala Glu  
 85 90 95

Ser

<210> 856  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 856  
 Gly Arg Met Ser His Ser Gly Val Cys Val Gly Gly Arg Thr Lys Val  
 1 5 10 15

Pro Pro Pro Leu Lys Met Pro Gly Val Leu Ala  
 20 25

<210> 857  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 857  
 Gly His Gln Thr Ala Pro Glu Thr Pro Ser Arg Ser Asp  
 1 5 10

<210> 858  
 <211> 5  
 <212> PRT  
 <213> Homo sapiens

<400> 858  
 Ser Gln Thr Asp Arg  
 1 5

<210> 859  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 859  
 Asn Ile Tyr Phe Lys Glu Lys Arg Lys Arg Gly Gly Ala Lys Met Ala  
 1 5 10 15

Gly Ala Ile Ile Glu Asn  
 20

455

<210> 860  
 <211> 147  
 <212> PRT  
 <213> Homo sapiens

<400> 860  
 Val Tyr Leu Cys Ala Tyr Thr Ser Thr Ile Asn Val Thr Val Thr Thr  
 1 5 10 15  
 Ala Asn Ala Lys Leu Ile Asn Met Cys Cys Leu Val Asp Ser Asn Thr  
 20 25 30  
 Arg Ser Cys Val Val Ile Asp Glu Gly Ile Phe Arg Ser Ala Glu Gln  
 35 40 45  
 Phe Leu Ile Lys Phe Arg Asn Lys Gln Ser Thr Ile Phe Pro Arg Phe  
 50 55 60  
 Thr Trp Glu Leu His Ser Ile Gly Leu Val Phe Ser Ile Val Phe Met  
 65 70 75 80  
 Gly Trp Cys Ile Gln Glu His Gln Ser Lys Asp Ile Gln Ile Pro His  
 85 90 95  
 Pro Ile Asp Ala Cys Glu Lys Gly Thr Val His Leu Asp Cys Asp Ala  
 100 105 110  
 Ala Pro Phe Pro Met Ala Phe Arg Tyr Leu Thr Asn Asp Glu Glu Asp  
 115 120 125  
 Asp Ser His Gly Ser Ala Gly Gln Gly Asp Lys His Glu Glu Leu Glu  
 130 135 140  
 Pro Lys Asn  
 145

<210> 861  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 861  
 Lys Met Pro Cys Arg Met Ser Pro Asn Ser Ser Ile Gln Val Gln Ser  
 1 5 10 15  
 Asn Pro Met Glu Asn His Ser Thr Gly Ile Leu Ile Lys Val Met Glu  
 20 25 30  
 Ile Pro Arg Ala Lys Met Thr Phe Ser Arg Ser Thr Gly Gly Arg Asp  
 35 40 45  
 Ile Met Val Ile Leu Leu Gln Tyr His Thr Ile Met Met Lys Met Leu  
 50 55 60  
 Gly Val Arg Lys Val Phe Met Ala Asn His Thr Leu Val Lys Pro Pro  
 65 70 75 80

456

Phe Trp Trp Ile Pro Thr Asn Arg Ile Ser Phe Ile Ser Pro Ile Pro  
                     85                    90                    95

Thr Leu Ile Phe Phe Phe Ser Phe Thr Gly Ser Arg Met Phe Lys Arg  
                     100                    105                    110

&lt;210&gt; 862

&lt;211&gt; 74

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 862

Thr Thr Lys Ser Glu Lys Met Gln Lys Ser Pro Trp Thr Phe Pro Trp  
   1                    5                    10                    15

Leu Thr Val Met Thr His Leu Leu Ser Gly Leu Lys Trp Pro Met Lys  
                     20                    25                    30

Glu Tyr His Gly Asn Ser Asn Ala Pro Ser His Leu Pro Arg Leu Gln  
                     35                    40                    45

Ser Met Arg Ala Val Thr Met Asn Val Met Ser Phe Leu Ser Trp Lys  
                     50                    55                    60

Leu Gly Leu Trp Pro Ile Ser Phe Thr Phe  
   65                    70

&lt;210&gt; 863

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 863

Ile Lys Phe Arg Asn Lys Gln Ser Thr Ile Phe Pro Arg Phe Thr Trp  
   1                    5                    10                    15

Glu Leu His Ser Ile Gly Leu Val Phe Ser Ile Val Phe Met Gly  
                     20                    25                    30

&lt;210&gt; 864

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 864

Ser Ser Ile Gln Val Gln Ser Asn Pro Met Glu Asn His Ser Thr Gly  
   1                    5                    10                    15

Ile Leu Ile Lys Val Met Glu Ile Pro Arg Ala Lys Met  
                     20                    25

457

<210> 865  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 865  
 Leu Gly Val Arg Lys Val Phe Met Ala Asn His Thr Leu Val Lys Pro  
 1 5 10 15

Pro Phe Trp Trp Ile Pro Thr Asn Arg Ile Ser Phe Ile Ser Pro Ile  
 20 25 30

Pro

<210> 866  
 <211> 9  
 <212> PRT  
 <213> Homo sapiens

<400> 866  
 Thr Met Ala Ser Met Gly Leu Gln Val  
 1 5

<210> 867  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<400> 867  
 Lys Ser Trp Met Met Leu Trp Ala Val Gln Asp Thr Gly Thr Ile Thr  
 1 5 10 15

Ile Arg Pro Ala Asn Arg Asn Thr Thr Pro Ala Thr Ile Met Val Leu  
 20 25 30

Ala Leu Ala Leu Ser Ser Ser Arg Gln Leu Val His Leu Pro Pro Thr  
 35 40 45

Thr Asp Ser Ser Thr Pro Arg Ala Ala Thr Met Met Leu Met Met Thr  
 50 55 60

Arg Ala Arg Ala Ala Cys Arg Ser Cys Gly Ser Ala Ser Ser Glu Ser  
 65 70 75 80

Tyr Thr Leu His Cys Ile Trp Pro Val Leu Cys Thr Thr Gln Phe Ile  
 85 90 95

His Arg Pro Ser Gln Met Val Cys Glu Val Thr Met Leu Leu Pro Met  
 100 105 110

Lys Ala Val Thr Arg His Met Gly Ser Ala Gln His Ser Met Thr Ala  
 115 120 125

Ser Gln Pro Arg Thr Ala Ser Ala Met Pro Ile Thr Cys Ser Pro Met

458

130 135 140  
Glu Ala Ile Val Gln Arg Pro Arg Glu Leu Arg Thr Trp Lys Ala Glu  
145 150 155 160  
Gly Ile Arg Leu Trp Gly Pro  
165

<210> 868  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 868  
Leu Gln Val Met Gly Ile Ala Leu Ala Val Leu Gly Trp Leu Ala Val  
1 5 10 15  
Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val Thr  
20 25

<210> 869  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 869  
Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu Gly Leu Trp Met Asn  
1 5 10 15  
Cys Val Val Gln Ser Thr  
20

<210> 870  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 870  
Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp  
1 5 10 15  
Leu Gln

<210> 871  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 871  
Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser Ala Lys Ala Lys Thr Met  
1 5 10 15  
Ile Val



459

<210> 872  
<211> 32  
<212> PRT  
<213> Homo sapiens

<400> 872  
Gly Val Val Phe Leu Leu Ala Gly Leu Met Val Ile Val Pro Val Ser  
1 5 10 15  
Trp Thr Ala His Asn Ile Ile Gln Asp Phe Tyr Asn Pro Leu Val Ala  
20 25 30

<210> 873  
<211> 12  
<212> PRT  
<213> Homo sapiens

<400> 873  
Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro Tyr  
1 5 10

<210> 874  
<211> 14  
<212> PRT  
<213> Homo sapiens

<400> 874  
Pro Phe Thr Ala Ile Ala Gly Ser Glu Ile Phe Ser Leu Glu  
1 5 10

<210> 875  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 875  
Ser Lys Thr Glu Ala Leu Thr Gln Ala Phe Arg  
1 5 10

<210> 876  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 876  
Val Val His Thr Val Ser Leu His Glu Ile Asp Val Ile Asn Ser Arg  
1 5 10 15

460

Thr Gln Gly Phe Leu Ala Leu Phe  
20

&lt;210&gt; 877

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 877

Pro Gly Val Leu Phe Ile Asp Glu Val His Met Leu Asp Ile Glu  
1 5 10 15

&lt;210&gt; 878

&lt;211&gt; 280

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (197)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 878

Ala Gly Ile Arg Gln Arg Phe Ser Ala Arg Leu Trp Gln Leu Val Ser  
1 5 10 15

Ile Met Ala Thr Val Thr Ala Thr Thr Lys Val Pro Glu Ile Arg Asp  
20 25 30

Val Thr Arg Ile Glu Arg Ile Gly Ala His Ser His Ile Arg Gly Leu  
35 40 45

Gly Leu Asp Asp Ala Leu Glu Pro Arg Gln Ala Ser Gln Gly Met Val  
50 55 60

Gly Gln Leu Ala Ala Arg Arg Ala Ala Gly Val Val Leu Glu Met Ile  
65 70 75 80

Arg Glu Gly Lys Ile Ala Gly Arg Ala Val Leu Ile Ala Gly Gln Pro  
85 90 95

Gly Thr Gly Lys Thr Ala Ile Ala Met Gly Met Ala Gln Ala Leu Gly  
100 105 110

Pro Asp Thr Pro Phe Thr Ala Ile Ala Gly Ser Glu Ile Phe Ser Leu  
115 120 125

Glu Met Ser Lys Thr Glu Ala Leu Thr Gln Ala Phe Arg Arg Ser Ile  
130 135 140

Gly Val Arg Ile Lys Glu Glu Thr Glu Ile Ile Glu Gly Glu Val Val  
145 150 155 160

Glu Ile Gln Ile Asp Arg Pro Ala Thr Gly Thr Gly Ser Lys Val Gly  
165 170 175

461

Lys Leu Thr Leu Lys Thr Thr Glu Met Glu Thr Ile Tyr Asp Leu Gly  
                   180                  185                  190  
 Thr Lys Met Ile Xaa Ser Leu Thr Lys Asp Lys Val Gln Ala Gly Asp  
                   195                  200                  205  
 Val Ile Thr Ile Asp Lys Ala Thr Gly Lys Ile Ser Lys Leu Gly Arg  
                   210                  215                  220  
 Ser Phe Thr Arg Ala Arg Glu Leu Arg Arg Tyr Gly Leu Pro Asp Gln  
                   225                  230                  235                  240  
 Val Arg Ala Val Pro Arg Trp Gly Ala Pro Glu Thr Gln Gly Gly Gly  
                   245                  250                  255  
 Ala His Arg Val Pro Ala Arg Asp Arg Arg His Gln Leu Ser His Pro  
                   260                  265                  270  
 Gly Leu Pro Gly Ala Leu Leu Arg  
                   275                  280

&lt;210&gt; 879

&lt;211&gt; 179

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (178)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 879

Ser Pro Ser Thr Arg Arg Arg Ala Arg Ser Pro Ser Trp Ala Ala Pro  
   1                  5                  10                  15  
 Ser His Ala Pro Ala Asn Tyr Asp Ala Met Gly Ser Gln Thr Lys Phe  
                   20                  25                  30  
 Val Gln Cys Pro Asp Gly Glu Leu Gln Lys Arg Lys Glu Val Val His  
                   35                  40                  45  
 Thr Val Ser Leu His Glu Ile Asp Val Ile Asn Ser Arg Thr Gln Gly  
                   50                  55                  60  
 Phe Leu Ala Leu Phe Ser Gly Asp Thr Gly Glu Ile Lys Ser Glu Val  
                   65                  70                  75                  80  
 Arg Glu Gln Ile Asn Ala Lys Val Ala Glu Trp Arg Glu Glu Gly Lys  
                   85                  90                  95  
 Ala Glu Ile Ile Pro Gly Val Leu Phe Ile Asp Glu Val His Met Leu  
                   100                  105                  110  
 Asp Ile Glu Ser Phe Ser Phe Leu Asn Arg Ala Leu Glu Ser Asp Met  
                   115                  120                  125  
 Ala Pro Val Gln Gln Val Tyr Gly Asp Ala Val Arg Ala Leu Val Ala

462

130 135 140

Gly Ala Pro Asp Ser Arg Asp Ala Thr Val Gly Gly Leu Val Pro Asn  
 145 150 155 160

Ser Cys Ser Pro Gly Asp Pro Leu Val Leu Glu Arg Pro Pro Pro Arg  
 165 170 175

Trp Xaa Ser

<210> 880  
 <211> 89  
 <212> PRT  
 <213> Homo sapiens

<400> 880

Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Ala Thr Asn Arg Gly  
 1 5 10 15

Ile Thr Arg Ile Arg Gly Thr Ser Tyr Gln Ser Pro His Gly Ile Pro  
 20 25 30

Ile Asp Leu Leu Asp Arg Arg His Val Thr Leu Gln Gly Pro Val Glu  
 35 40 45

Glu Gly Glu Ala Leu Asp Val Gln His Val Asp Leu Val Asp Glu Gln  
 50 55 60

His Ser Arg Asp Asp Leu Arg Leu Ala Leu Leu Ala Pro Leu Ser His  
 65 70 75 80

Leu Gly Ile Asp Leu Leu Thr Asp Phe  
 85

<210> 881  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 881

Tyr Asp Ala Met Gly Ser Gln Thr Lys Phe Val Gln Cys Pro Asp Gly  
 1 5 10 15

Glu Leu Gln Lys Arg Lys Glu Val Val His Thr Val Ser Leu  
 20 25 30

<210> 882  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 882

Lys Ala Glu Ile Ile Pro Gly Val Leu Phe Ile Asp Glu Val His Met  
 1 5 10 15

463

Leu Asp Ile Glu Ser Phe Ser Phe Leu Asn Arg Ala Leu Glu Ser  
20 25 30

&lt;210&gt; 883

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 883

Glu Ala Thr Asn Arg Gly Ile Thr Arg Ile Arg Gly Thr Ser Tyr Gln  
1 5 10 15

Ser Pro His Gly Ile Pro Ile Asp Leu Leu Asp Arg  
20 25

&lt;210&gt; 884

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 884

Met Arg Ser Ala Arg Pro Ser Leu Gly Cys Leu Pro Ser Trp Ala Phe  
1 5 10 15

Ser Gln Ala Leu Asn Ile  
20

&lt;210&gt; 885

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 885

Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys  
1 5 10 15

Glu Lys Gly Asn Phe Asn  
20

&lt;210&gt; 886

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 886

Val Ala His Gly Leu Ala Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu  
1 5 10 15

Ile Leu Pro Glu Leu Gln Ala Arg Ile Arg  
20 25

&lt;210&gt; 887

464

<211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 887  
 Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln  
 1 5 10 15

Arg Cys

<210> 888  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<400> 888  
 Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met Ala  
 1 5 10 15

Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly Asp  
 20 25 30

Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn  
 35 40

<210> 889  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<400> 889  
 Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val  
 1 5 10 15

Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser Gln Tyr  
 20 25 30

Ser Gln Ala Gly Phe Ser Gly Glu Asp Arg Leu Glu Gln  
 35 40 45

<210> 890  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<400> 890  
 Ala Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro  
 1 5 10 15

Glu Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp  
 20 25 30

Asp Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln  
 35 40 45

465

Glu Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val  
 50 55 60

Pro Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ile Ser Gly  
 65 70 75 80

Met Glu Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser  
 85 90

&lt;210&gt; 891

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 891

Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile Ser Ala Val Cys  
 1 5 10 15

Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala Trp Ser Tyr Tyr  
 20 25 30

Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu  
 35 40

&lt;210&gt; 892

&lt;211&gt; 76

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 892

Leu Arg Leu His Ser Glu Lys Leu Pro Leu Ala Ala Arg Ser Ala Gly  
 1 5 10 15

Pro Ser Leu Leu Val Ile Ile Gln Ser Ser Gln Cys Pro Gly Gly Arg  
 20 25 30

Arg Tyr Arg Gly Ser Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys  
 35 40 45

Pro Leu Arg Arg Gly Ala Leu Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr  
 50 55 60

Ser Leu Pro Asn Ala Val Gly Pro Pro Phe Thr Trp  
 65 70 75

&lt;210&gt; 893

&lt;211&gt; 133

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 893

Val Trp Leu Thr Pro Thr Phe Ala Ser Trp Ile Asn Cys Pro Ser Arg  
 1 5 10 15

466

Pro Val Thr Val Leu Ala Ser Arg Ile Gly Phe Thr Ala Thr Ala Ser  
                   20                  25                  30  
 Met Ser Phe Trp Arg Thr Gly Ser Gly Arg Ala Pro Val Ser Trp Ser  
           35                  40                  45  
 Thr Pro Pro Pro Cys Arg Leu Cys Leu Pro Cys His Asn Thr Val Lys  
       50                  55                  60  
 Leu Ala Leu Ala Gly Arg Ile Gly Leu Ser Arg Pro Asn Ser Ser Ala  
       65                  70                  75                  80  
 Gly His Leu Arg Thr Ser Trp Gln Met Pro Leu Ser Leu Arg Thr Thr  
                   85                  90                  95  
 Ala Ala Ser Leu Pro Thr Arg Asn Leu Gln Met Thr Ala Ala Ser Arg  
           100                  105                  110  
 Cys Pro Arg Arg Phe Ser Gly Thr Cys Gly Arg Arg Lys Arg Lys Arg  
           115                  120                  125  
 Leu Leu Trp Ala Ala  
       130

<210> 894  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 894  
 Gly Val Cys Gln Val Ser Phe Met Gly Pro Ser Arg Pro Thr Pro His  
       1                  5                  10                  15  
 Pro Ser Pro Leu Pro Leu Pro Gly Asp Ala Glu Leu Ser Gln Trp Tyr  
           20                  25                  30  
 Gln Gln Ala Pro Ser Pro Ser Gly Ser Trp Ser Cys Ser Ile Ile Gly  
           35                  40                  45  
 Glu Pro Gln Gln Lys Asn Gly Glu Glu Glu Ala Glu Phe Gly Val  
       50                  55                  60  
 Leu Asn Pro Pro Ala Pro Thr Leu Gln His Gln Gly Cys Tyr Gly Leu  
       65                  70                  75                  80  
 Ser Cys Arg Ala Thr Leu Ala  
           85

<210> 895  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 895  
 Thr Met Lys Leu Leu Lys Leu Arg Arg Asn Ile Val Lys Leu Ser Leu  
       1                  5                  10                  15



467

Tyr Arg His Phe Thr Asn  
20

<210> 896  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 896  
Thr Leu Ile Leu Ala Val Ala Ala Ser Ile Val Phe Ile Ile Trp Thr  
1 5 10 15

Thr Met Lys Phe Arg Ile  
20

<210> 897  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 897  
Val Thr Cys Gln Ser Asp Trp Arg Glu Leu Trp Val Asp Asp Ala Ile  
1 5 10 15

Trp Arg Leu Leu Phe Ser Met Ile Leu Phe Val Ile  
20 25

<210> 898  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 898  
Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe Ser  
1 5 10 15

Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln  
20 25

<210> 899  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 899  
Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe Ser  
1 5 10 15

Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln  
20 25

<210> 900

468

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 900

Lys Glu Pro Met Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser  
1 5 10 15

Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu  
20 25 30

Asp Asp Leu  
35

&lt;210&gt; 901

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 901

Lys Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp Val Ala Leu  
1 5 10 15

Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr His Phe Glu  
20 25 30

Arg Ser Lys Met Glu  
35

&lt;210&gt; 902

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 902

Asp Pro Arg Val Arg Leu Asn Ser Leu Thr Cys Lys His Ile Phe Ile  
1 5 10 15

Ser Leu Thr Gln  
20

&lt;210&gt; 903

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 903

Asn Ala Phe Gly Arg His Ser Thr Ala Val Lys  
1 5 10

&lt;210&gt; 904

&lt;211&gt; 283

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 904

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Ser | Cys | Leu | Leu | Cys | Gly | Ile | Ser | Glu | Tyr | Pro | Ile | Gln | Arg | Xaa |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     | 15  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Cys | Pro | Gly | Cys | Phe | Asp | Pro | Cys | Arg | Xaa | Ala | Phe | Ser | Ser | Glu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Leu | Thr | Gly | Ser | Asn | Pro | Gly | His | His | Ser | Gln | Ser | Gly | Ile | Trp |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Arg | Gln | Ala | Thr | Pro | Gly | Val | Thr | Leu | His | Lys | Val | Val | Val | Ala |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Ala | Leu | Tyr | Leu | Leu | Phe | Ser | Gly | Met | Glu | Gly | Val | Leu | Arg | Val |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Ala | Gln | Thr | Asp | Leu | Ala | Ser | Leu | Ala | Phe | Ile | Pro | Leu | Ala |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Asp | Thr | Ala | Leu | Cys | Trp | Trp | Ile | Phe | Ile | Ser | Leu | Thr | Gln |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Met | Lys | Leu | Leu | Lys | Leu | Arg | Arg | Asn | Ile | Val | Lys | Leu | Ser | Leu |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Arg | His | Phe | Thr | Asn | Thr | Leu | Ile | Leu | Ala | Val | Ala | Ala | Ser | Ile |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Phe | Ile | Ile | Trp | Thr | Thr | Met | Lys | Phe | Arg | Ile | Val | Thr | Cys | Gln |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Trp | Arg | Glu | Leu | Trp | Val | Asp | Asp | Ala | Ile | Trp | Arg | Leu | Leu |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ser | Met | Ile | Leu | Phe | Val | Ile | Met | Val | Leu | Trp | Arg | Pro | Ser | Ala |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Asn | Gln | Arg | Phe | Ala | Phe | Ser | Pro | Leu | Ser | Glu | Glu | Glu | Glu | Glu |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Glu | Gln | Lys | Glu | Pro | Met | Leu | Lys | Glu | Ser | Phe | Glu | Gly | Met | Lys |
|     | 210 |     |     |     |     | 215 |     |     |     |     |     | 220 |     |     |     |

470

Met Arg Ser Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys  
225 230 235 240

Ala Gln Glu Asp Asp Leu Lys Trp Val Glu Glu Asn Val Pro Ser Ser  
245 250 255

Val Thr Asp Val Ala Leu Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg  
260 265 270

Met Ile Thr His Phe Glu Arg Ser Lys Met Glu  
275 280

<210> 905

<211> 13

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 905

Tyr Glu Pro Met Asp Phe Xaa Met Ala Leu Ile Tyr Asp  
1 5 10

<210> 906

<211> 16

<212> PRT

<213> Homo sapiens

<400> 906

Ile Arg His Glu Leu Thr Val Leu Arg Asp Thr Arg Pro Ala Cys Ala  
1 5 10 15

<210> 907

<211> 10

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (4)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 907

Met Asp Phe Xaa Met Ala Leu Ile Tyr Asp  
1 5 10

<210> 908

471

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 908

Met Gln Glu Met Met Arg Asn Gln Asp Arg Ala Leu Ser Asn Leu Glu  
1 5 10 15

Ser Ile Pro Gly Gly Tyr Asn Ala  
20

&lt;210&gt; 909

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 909

Leu Arg Arg Met Tyr Thr Asp Ile Gln Glu Pro Met Leu Ser Ala Ala  
1 5 10 15

Gln Glu Gln Phe Gly Gly Asn Pro Phe  
20 25

&lt;210&gt; 910

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 910

Ala Ser Leu Val Ser Asn Thr Ser Ser Gly Glu Gly Ser Gln Pro Ser  
1 5 10 15

Arg Thr Glu Asn Arg Asp Pro Leu Pro Asn Pro Trp Ala Pro Gln Thr  
20 25 30

&lt;210&gt; 911

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 911

Ser Gln Ser Ser Ser Ala Ser Ser Gly Thr Ala Ser Thr Val Gly Gly  
1 5 10 15

Thr Thr Gly Ser Thr Ala Ser Gly Thr Ser Gly Gln Ser Thr Thr Ala  
20 25 30

Pro Asn Leu Val Pro Gly Val Gly Ala Ser Met Phe Asn Thr Pro Gly  
35 40 45

Met Gln Ser Leu Leu Gln Gln Ile Thr Glu Asn Pro Gln Leu Met Gln  
50 55 60

472

Asn Met Leu Ser Ala Pro Tyr  
65 70

<210> 912  
<211> 45  
<212> PRT  
<213> Homo sapiens

<400> 912  
Met Arg Ser Met Met Gln Ser Leu Ser Gln Asn Pro Asp Leu Ala Ala  
1 5 10 15  
Gln Met Met Leu Asn Asn Pro Leu Phe Ala Gly Asn Pro Gln Leu Gln  
20 25 30  
Glu Gln Met Arg Gln Gln Leu Pro Thr Phe Leu Gln Gln  
35 40 45

<210> 913  
<211> 73  
<212> PRT  
<213> Homo sapiens

<400> 913  
Met Gln Asn Pro Asp Thr Leu Ser Ala Met Ser Asn Pro Arg Ala Met  
1 5 10 15  
Gln Ala Leu Leu Gln Ile Gln Gln Gly Leu Gln Thr Leu Ala Thr Glu  
20 25 30  
Ala Pro Gly Leu Ile Pro Gly Phe Thr Pro Gly Leu Gly Ala Leu Gly  
35 40 45  
Ser Thr Gly Gly Ser Ser Gly Thr Asn Gly Ser Asn Ala Thr Pro Ser  
50 55 60  
Glu Asn Thr Ser Pro Thr Ala Gly Thr  
65 70

<210> 914  
<211> 72  
<212> PRT  
<213> Homo sapiens

<400> 914  
Thr Glu Pro Gly His Gln Gln Phe Ile Gln Gln Met Leu Gln Ala Leu  
1 5 10 15  
Ala Gly Val Asn Pro Gln Leu Gln Asn Pro Glu Val Arg Phe Gln Gln  
20 25 30  
Gln Leu Glu Gln Leu Ser Ala Met Gly Phe Leu Asn Arg Glu Ala Asn  
35 40 45

473

Leu Gln Ala Leu Ile Ala Thr Gly Gly Asp Ile Asn Ala Ala Ile Glu  
50 55 60

Arg Leu Leu Gly Ser Gln Pro Ser  
65 70

<210> 915  
<211> 45  
<212> PRT  
<213> Homo sapiens

<400> 915  
Arg Asn Pro Ala Met Met Gln Glu Met Met Arg Asn Gln Asp Arg Ala  
1 5 10 15

Leu Ser Asn Leu Glu Ser Ile Pro Gly Gly Tyr Asn Ala Leu Arg Arg  
20 25 30

Met Tyr Thr Asp Ile Gln Glu Pro Met Leu Ser Ala Ala  
35 40 45

<210> 916  
<211> 13  
<212> PRT  
<213> Homo sapiens

<400> 916  
Gly Asn Pro Phe Ala Ser Leu Val Ser Asn Thr Ser Ser  
1 5 10

<210> 917  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 917  
Glu Asn Arg Asp Pro Leu Pro Asn Pro Trp Ala  
1 5 10

<210> 918  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 918  
Gly Lys Ile Leu Lys Asp Gln Asp Thr Leu Ser Gln His Gly Ile His  
1 5 10 15

Asp

<210> 919  
<211> 14

474

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 919

Gly Leu Thr Val His Leu Val Ile Lys Thr Gln Asn Arg Pro  
1 5 10

&lt;210&gt; 920

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 920

Ser Glu Leu Gln Ser Gln Met Gln Arg Gln Leu Leu Ser Asn Pro Glu  
1 5 10 15

Met Met

&lt;210&gt; 921

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 921

Pro Glu Ile Ser His Met Leu Asn Asn Pro Asp Ile Met Arg  
1 5 10

&lt;210&gt; 922

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 922

Arg Gln Leu Ile Met Ala Asn Pro Gln Met Gln Gln Leu Ile Gln Arg  
1 5 10 15

Asn Pro

&lt;210&gt; 923

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 923

Asn Leu Cys His Val Asp Cys Gln Asp Leu Leu Asn Pro Asn Leu Leu  
1 5 10 15

Ala Gly Ile His Cys Ala Lys Arg Ile Val Ser  
20 25

&lt;210&gt; 924



475

<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 924  
Leu Asp Gly Phe Glu Gly Tyr Ser Leu Ser Asp Trp Leu Cys Leu Ala  
1 5 10 15  
Phe Val Glu Ser Lys Phe Asn  
20

<210> 925  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 925  
Asn Glu Asn Ala Asp Gly Ser Phe Asp Tyr Gly Leu Phe Gln Ile Asn  
1 5 10 15  
Ser His Tyr Trp Cys Asn  
20

<210> 926  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 926  
Asn Leu Cys His Val Asp Cys Gln Asp Leu Leu Asn Pro Asn Leu Leu  
1 5 10 15  
Ala Gly Ile His Cys Ala Lys Arg Ile Val Ser  
20 25

<210> 927  
<211> 13  
<212> PRT  
<213> Homo sapiens

<400> 927  
Glu Pro Ser Ala Leu Ser Cys Thr Ser Ser Pro Pro Arg  
1 5 10

<210> 928  
<211> 13  
<212> PRT  
<213> Homo sapiens

<400> 928  
Ile Arg Glu Val Asn Glu Val Ile Gln Asn Pro Ala Thr  
1 5 10

476

&lt;210&gt; 929

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 929

Ile Thr Arg Ile Leu Leu Ser His Phe Asn Trp Asp Lys Glu Lys Leu  
 1 5 10 15

Met Glu Arg Tyr Phe Asp Gly Asn Leu Glu Lys Leu Phe Ala  
 20 25 30

&lt;210&gt; 930

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 930

Asn Thr Arg Ser Ser Ala Gln Asp Met Pro Cys Gln Ile Cys Tyr Leu  
 1 5 10 15

Asn Tyr Pro Asn Ser Tyr Phe  
 20

&lt;210&gt; 931

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 931

Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg Leu Ile Thr Asp  
 1 5 10 15

Ser Lys Val Lys Leu Lys Tyr Gln His Leu Ile Thr Asn Ser Phe Val  
 20 25 30

Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro Ala Pro Asp Cys His His  
 35 40 45

Val Val Lys Val Gln Tyr Pro Asp Ala Lys Pro Val  
 50 55 60

&lt;210&gt; 932

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 932

Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg Leu Ile Thr Asp  
 1 5 10 15

Ser Lys Val Lys Leu Lys Tyr Gln His Leu Ile Thr Asn Ser Phe Val  
 20 25 30

Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro Ala Pro Asp Cys His His

477

35                                      40                                      45  
 Val Val Lys Val  
 50

<210> 933  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 933  
 Gly Cys Asn His Met Val Cys Arg Asn Gln Asn Cys Lys Ala Glu Phe  
 1                                      5                                      10                                      15  
 Cys Trp Val Cys Leu Gly Pro Trp Glu Pro His Gly Ser Ala Trp Tyr  
 20                                      25                                      30  
 Asn Cys Asn Arg Tyr Asn Glu Asp Asp Ala Lys Ala Ala Arg Asp Ala  
 35                                      40                                      45  
 Gln Glu Arg Ser Arg Ala Ala Leu Gln Arg Tyr Leu  
 50                                      55                                      60

<210> 934  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 934  
 Phe Tyr Cys Asn Arg Tyr Met Asn His Met Gln Ser Leu Arg Phe Glu  
 1                                      5                                      10                                      15  
 His Lys Leu Tyr Ala Gln Val Lys Gln Lys Met Glu Glu Met Gln Gln  
 20                                      25                                      30  
 His Asn Met Ser Trp Ile Glu Val Gln Phe Leu Lys Lys Ala Val Asp  
 35                                      40                                      45  
 Val Leu Cys Gln Cys Arg Ala Thr Leu Met Tyr Thr  
 50                                      55                                      60

<210> 935  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 935  
 Tyr Val Phe Ala Phe Tyr Leu Lys Lys Asn Asn Gln Ser Ile Ile Phe  
 1                                      5                                      10                                      15  
 Glu Asn Asn Gln Ala Asp Leu Glu Asn Ala Thr Glu Val Leu Ser Gly  
 20                                      25                                      30  
 Tyr Leu Glu Arg Asp Ile Ser Gln Asp Ser Leu Gln Asp Ile Lys Gln  
 35                                      40                                      45

478

Lys Val Gln Asp Lys Tyr Arg Tyr Cys Glu Ser Arg  
 50 55 60

&lt;210&gt; 936

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 936

Thr Gly Leu Glu Cys Gly His Lys Phe Cys Met Gln Cys Trp Ser Glu  
 1 5 10 15

Tyr Leu Thr Thr Lys Ile Met Glu Glu Gly Met Gly Gln Thr Ile Ser  
 20 25 30

Cys Pro Ala His Gly  
 35

&lt;210&gt; 937

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 937

Met Trp Gly Tyr Leu Phe Val Asp Ala Ala Trp Asn Phe Leu Gly Cys  
 1 5 10 15

Leu Ile Cys Gly Trp  
 20

&lt;210&gt; 938

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 938

Met His Phe Ile Ser Ser Gly Asn Val Ser Ala Ile Arg Ser Ser Ile  
 1 5 10 15

Leu Leu Leu Arg Xaa Ser Leu Ser Tyr Leu Gly Asn Cys Leu Arg Val  
 20 25 30

Ser Ala Ile Phe Val Tyr Phe Leu Leu Phe Leu Leu Ser  
 35 40 45

&lt;210&gt; 939

&lt;211&gt; 80

&lt;212&gt; PRT

479

&lt;213&gt; Homo sapiens

&lt;400&gt; 939

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Met Asp Gln Ala Leu Arg Gly Ser Pro Ser Glu Gly Phe Ser Thr Asp
 1             5             10             15

Pro Ser Pro Pro Gln Val Gly Arg Gln Ile Pro Ser Phe Pro Pro Trp
          20             25             30

Arg Arg Leu Val Leu Pro Lys Ala Ser Gly Cys Phe Leu Glu Arg Glu
 35             40             45

Trp Trp Leu Cys Val Phe Lys Leu Arg Thr Arg Pro Gly Ala Glu Ala
 50             55             60

His Ala Tyr Asn Ser Ser Ile Leu Gly Gly Arg Gly Lys Gly Ile Thr
 65             70             75             80

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&lt;210&gt; 940

&lt;211&gt; 131

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 940

```

Met Leu Pro Ala Leu Ala Ser Cys Cys His Phe Ser Pro Pro Glu Gln
 1             5             10             15

Ala Ala Arg Leu Lys Lys Leu Gln Glu Gln Lys Gln Gln Lys Val
 20             25             30

Glu Phe Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp
 35             40             45

Ser Gly Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg
 50             55             60

Ser Ile Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser
 65             70             75             80

Phe Gly Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu
 85             90             95

Phe Ala Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu
 100            105            110

Trp Asp Pro Gln Lys Ala Glu Glu Lys Arg Asn Xaa Lys Glu Leu Ala
 115            120            125

Gln Arg Gln

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480

130

<210> 941  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 941  
 Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser Pro Ala Ser  
   1                  5                  10                  15  
 Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly Ala Ala Lys  
           20                  25                  30  
 Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly Cys Xaa Pro  
       35                  40                  45  
 Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala Met Asn Glu  
       50                  55                  60  
 Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu  
       65                  70                  75

<210> 942  
 <211> 40  
 <212> PRT  
 <213> Homo sapiens

<400> 942  
 Pro Pro Arg Arg Pro Ala Gln Leu Pro Leu Thr Pro Gly Ala Gly Gln  
   1                  5                  10                  15  
 Gly Ala Gly Arg Asp Lys Ala Ala Ala Ile Arg Ala His Pro Gly Ala  
           20                  25                  30  
 Pro Pro Leu Asn His Leu Leu Pro  
       35                  40

<210> 943  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 943  
 Ala Val Pro Gln Ala Gly Gly Lys Gln Val Phe Asp Leu Ser Pro Leu  
   1                  5                  10                  15  
 Glu Leu Gly Tyr Val Arg Gly Met Cys Val Cys Val  
       20                  25

481

<210> 944  
 <211> 207  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (124)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (178)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 944  
 Met Leu Pro Ala Leu Ala Ser Cys Cys His Phe Ser Pro Pro Glu Gln  
 1 5 10 15  
 Ala Ala Arg Leu Lys Lys Leu Gln Glu Gln Glu Lys Gln Gln Lys Val  
 20 25 30  
 Glu Phe Arg Lys Arg Met Glu Lys Glu Val Ser Asp Phe Ile Gln Asp  
 35 40 45  
 Ser Gly Gln Ile Lys Lys Lys Phe Gln Pro Met Asn Lys Ile Glu Arg  
 50 55 60  
 Ser Ile Leu His Asp Val Val Glu Val Ala Gly Leu Thr Ser Phe Ser  
 65 70 75 80  
 Phe Gly Glu Asp Asp Asp Cys Arg Tyr Val Met Ile Phe Lys Lys Glu  
 85 90 95  
 Phe Ala Pro Ser Asp Glu Glu Leu Asp Ser Tyr Arg Arg Gly Glu Glu  
 100 105 110  
 Trp Asp Pro Gln Lys Ala Glu Glu Lys Arg Asn Xaa Lys Glu Leu Ala  
 115 120 125  
 Gln Arg Gln Glu Glu Glu Ala Ala Gln Gln Gly Pro Val Val Val Ser  
 130 135 140  
 Pro Ala Ser Asp Tyr Lys Asp Lys Tyr Ser His Leu Ile Gly Lys Gly  
 145 150 155 160  
 Ala Ala Lys Asp Ala Ala His Met Leu Gln Ala Asn Lys Thr Tyr Gly  
 165 170 175  
 Cys Xaa Pro Val Ala Asn Lys Arg Asp Thr Arg Ser Ile Glu Glu Ala  
 180 185 190  
 Met Asn Glu Ile Arg Ala Lys Lys Arg Leu Arg Gln Ser Gly Glu  
 195 200 205

<210> 945

482

<211> 34  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 945  
 Leu Leu Cys Pro Val Leu Asn Ser Gly Xaa Ser Trp Asn Phe Pro His  
 1 5 10 15  
 Pro Ser Gln Pro Glu Tyr Ser Phe His Gly Phe His Ser Thr Arg Leu  
 20 25 30

Trp Ile

<210> 946  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 946  
 Pro Ser Thr Pro Trp Phe Leu Phe Leu Leu Gly Leu Thr Cys Pro Phe  
 1 5 10 15  
 Ser Thr Ser His Pro Arg Trp Asp Ser Ile Pro Pro  
 20 25

<210> 947  
 <211> 227  
 <212> PRT  
 <213> Homo sapiens

<400> 947  
 Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu  
 1 5 10 15  
 Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu  
 20 25 30  
 Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys  
 35 40 45  
 Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser  
 50 55 60  
 Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu  
 65 70 75 80  
 Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr  
 85 90 95  
 Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp



483

|   |     |     |
|---|-----|-----|
| 100   | 105 | 110 |
| Gly Ala Ser Ile Val Cys Ser Val Asn His Glu Ser Leu Lys Gly Ala |     |     |
| 115   | 120 | 125 |
| Asp Arg Ser Thr Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala |     |     |
| 130   | 135 | 140 |
| Met Ile Arg Pro Asp Pro Pro His Pro Arg Glu Gly Gln Lys Leu Leu |     |     |
| 145   | 150 | 155 |
| Leu His Cys Glu Gly Arg Gly Asn Pro Val Pro Gln Gln Tyr Leu Trp |     |     |
| 165   | 170 | 175 |
| Glu Lys Glu Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser Ala |     |     |
| 180   | 185 | 190 |
| Leu Ile Phe Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys |     |     |
| 195   | 200 | 205 |
| Thr Ala Thr Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu Asn |     |     |
| 210   | 215 | 220 |
| Val Asn Asp   |     |     |
| 225   |     |     |

<210> 948  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<400> 948  
 Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu  
 1 5 10 15  
 Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu  
 20 25 30  
 Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys  
 35 40 45  
 Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser  
 50 55 60

<210> 949  
 <211> 65  
 <212> PRT  
 <213> Homo sapiens

<400> 949  
 Cys Gln Ser Ser Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg Lys  
 1 5 10 15

484

Gly Asp Gln Glu Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp Pro  
                   20                                  25                                  30  
 Asn Gly Lys Thr Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val Thr  
                   35                                  40                                  45  
 Arg Glu Asp Asp Gly Ala Ser Ile Val Cys Ser Val Asn His Glu Ser  
                   50                                  55                                  60  
 Leu  
                   65

<210> 950  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<400> 950  
 His Glu Ser Leu Lys Gly Ala Asp Arg Ser Thr Ser Gln Arg Ile Glu  
                   1                                  5                                  10                                  15  
 Val Leu Tyr Thr Pro Thr Ala Met Ile Arg Pro Asp Pro Pro His Pro  
                   20                                  25                                  30  
 Arg Glu Gly Gln Lys Leu Leu Leu His Cys Glu Gly Arg Gly Asn Pro  
                   35                                  40                                  45  
 Val Pro Gln Gln Tyr Leu Trp Glu Lys Glu  
                   50                                  55

<210> 951  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<400> 951  
 Trp Glu Lys Glu Gly Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser  
                   1                                  5                                  10                                  15  
 Ala Leu Ile Phe Pro Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly  
                   20                                  25                                  30  
 Cys Thr Ala Thr Ser Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu  
                   35                                  40                                  45  
 Asn Val Asn Asp  
                   50

<210> 952  
 <211> 36  
 <212> PRT  
 <213> Homo sapiens

<400> 952  
 Pro Ser Pro Val Pro Ser Ser Ser Ser Thr Tyr His Ala Ile Ile Gly

485

1                    5                    10                    15  
 Gly Ile Val Ala Phe Ile Val Phe Leu Leu Leu Ile Met Leu Ile Phe  
                     20                    25                    30  
 Leu Gly His Tyr  
                     35

<210> 953  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 953  
 Leu Ile Arg His Lys Gly Thr Tyr Leu Thr His Glu Ala Lys Gly Ser  
   1                    5                    10                    15  
 Asp Asp Ala Pro Asp Ala Asp Thr Ala Ile Ile Asn Ala Glu Gly Gly  
                     20                    25                    30  
 Gln Ser Gly Gly Asp Asp Lys Lys Glu Tyr Phe Ile  
                     35                    40

<210> 954  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<400> 954  
 Val Pro Glu Leu Pro Asp Arg Val His Gln Leu His Gln Ala Val Gln  
   1                    5                    10                    15  
 Gly Cys Ala Leu Gly Arg Pro Gly Phe Pro Gly Gly Pro Thr His Ser  
                     20                    25                    30  
 Gly His His Lys Ser His Pro Gly Pro Ala Gly Gly Asp Tyr Asn Arg  
                     35                    40                    45  
 Cys Asp Arg Pro Gly Gln Val His Leu His Asn Pro Arg Gly Thr Gly  
                     50                    55                    60  
 Arg Arg Gly Gln Leu His Pro Thr Ala Gly Pro Gly Val His Arg Arg  
                     65                    70                    75                    80  
 Ala Cys Pro Ser Gln Gln Leu Pro His Arg Leu Gly Pro Gly Val Pro  
                     85                    90                    95  
 Cys Pro Ser Pro Ser Leu Thr Pro Val Leu Pro Ser Trp Thr Gln Ser  
                     100                    105                    110  
 Trp Cys Gly Leu Pro Gly Tyr Thr Ser Ser Ser  
                     115                    120

<210> 955  
 <211> 22

486

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 955

Val His Gln Leu His Gln Ala Val Gln Gly Cys Ala Leu Gly Arg Pro  
 1 5 10 15

Gly Phe Pro Gly Gly Pro  
 20

&lt;210&gt; 956

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 956

Pro Thr His Ser Gly His His Lys Ser His Pro Gly Pro Ala Gly Gly  
 1 5 10 15

Asp Tyr Asn Arg Cys Asp Arg Pro Gly Gln Val His Leu His Asn Pro  
 20 25 30

Arg Gly Thr Gly Arg Arg Gly Gln Leu His  
 35 40

&lt;210&gt; 957

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 957

Leu His Pro Thr Ala Gly Pro Gly Val His Arg Arg Ala Cys Pro Ser  
 1 5 10 15

Gln Gln Leu Pro His Arg Leu Gly Pro Gly Val Pro Cys Pro Ser Pro  
 20 25 30

Ser Leu Thr Pro Val Leu Pro Ser Trp Thr Gln Ser Trp Cys Gly Leu  
 35 40 45

Pro Gly Tyr Thr Ser Ser Ser  
 50 55

&lt;210&gt; 958

&lt;211&gt; 276

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 958

Ser Leu Arg Arg Pro Arg Ser Ala Ala Xaa Gln Thr Leu Thr Thr Phe

487

| 1   | 5   | 10  | 15  |
|---|-----|-----|-----|
| Leu Ser Ser Val Ser Ser Ala Ser Ser Ser Ala Leu Pro Gly Ser Arg | 20  | 25  | 30  |
| Glu Pro Cys Asp Pro Arg Ala Pro Pro Pro Pro Arg Ser Gly Ser Ala | 35  | 40  | 45  |
| Ala Ser Cys Cys Ser Cys Cys Cys Ser Cys Pro Arg Arg Arg Ala Pro | 50  | 55  | 60  |
| Leu Arg Ser Pro Arg Gly Ser Lys Arg Arg Ile Arg Gln Arg Glu Val | 65  | 70  | 75  |
| Val Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly Val Pro | 85  | 90  | 95  |
| Gly Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly | 100 | 105 | 110 |
| Ile Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg | 115 | 120 | 125 |
| Glu Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp | 130 | 135 | 140 |
| Ser Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr | 145 | 150 | 155 |
| Phe Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly | 165 | 170 | 175 |
| Ser Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe | 180 | 185 | 190 |
| Thr Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile | 195 | 200 | 205 |
| Ile Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile | 210 | 215 | 220 |
| His Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly | 225 | 230 | 235 |
| Leu Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys | 245 | 250 | 255 |
| Gly Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu | 260 | 265 | 270 |
| Glu Leu Pro Lys   | 275 |     |     |

&lt;210&gt; 959

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

488

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 959

Ser Leu Arg Arg Pro Arg Ser Ala Ala Xaa Gln Thr Leu Thr Thr Phe  
 1 5 10 15

Leu Ser Ser Val Ser Ser Ala Ser Ser Ser Ala Leu Pro Gly Ser Arg  
 20 25 30

Glu Pro Cys Asp Pro Arg Ala Pro Pro Pro Pro Arg Ser Gly Ser Ala  
 35 40 45

Ala Ser Cys Cys Ser Cys Cys Cys Ser Cys Pro Arg Arg  
 50 55 60

&lt;210&gt; 960

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 960

Arg Ala Pro Leu Arg Ser Pro Arg Gly Ser Lys Arg Arg Ile Arg Gln  
 1 5 10 15

Arg Glu Val Val Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala  
 20 25 30

Gly Val Pro Gly Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly  
 35 40 45

Thr Pro Gly Ile  
 50

&lt;210&gt; 961

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 961

Thr Pro Gly Ile Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu  
 1 5 10 15

Cys Leu Arg Glu Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln  
 20 25 30

Cys Ser Trp Ser Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala  
 35 40 45

Glu Cys Thr Phe  
 50

489

<210> 962  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<400> 962  
 Phe Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly  
     1                    5                    10                    15  
 Ser Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe  
             20                    25                    30  
 Thr Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile  
             35                    40                    45  
 Ile Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile  
             50                    55                    60  
 His Arg  
     65

<210> 963  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 963  
 Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu  
     1                    5                    10                    15  
 Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly  
             20                    25                    30  
 Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu Glu  
             35                    40                    45  
 Leu Pro Lys  
     50

<210> 964  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 964  
 Thr Lys Lys Glu Asn Cys Arg Pro Ala Ser Leu Met Asn Ile Asp Thr  
     1                    5                    10                    15  
 Lys Ile Leu Asn Lys Ile Leu Met Asn Gln  
             20                    25

<210> 965  
 <211> 214  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (26)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (90)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (94)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (105)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (120)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 965  
 Met Cys Asn Leu Pro Ile Lys Val Val Cys Arg Ala Asn Ala Glu Tyr  
 1 5 10 15  
 Met Ser Pro Ser Gly Lys Val Pro Xaa Xaa His Val Gly Asn Gln Val  
 20 25 30  
 Val Ser Glu Leu Gly Pro Ile Val Gln Phe Val Lys Ala Lys Gly His  
 35 40 45  
 Ser Leu Ser Asp Gly Leu Glu Glu Val Gln Lys Ala Glu Met Lys Ala  
 50 55 60  
 Tyr Met Glu Leu Val Asn Asn Met Leu Leu Thr Ala Glu Leu Tyr Leu  
 65 70 75 80  
 Gln Trp Cys Asp Glu Ala Thr Val Gly Xaa Ile Thr His Xaa Arg Tyr  
 85 90 95  
 Gly Ser Pro Tyr Pro Trp Pro Leu Xaa His Ile Leu Ala Tyr Gln Lys  
 100 105 110  
 Gln Trp Glu Val Lys Arg Lys Xaa Lys Ala Ile Gly Trp Gly Lys Lys  
 115 120 125  
 Thr Leu Asp Gln Val Leu Glu Asp Val Asp Gln Cys Cys Gln Ala Leu  
 130 135 140



491

Ser Gln Arg Leu Gly Thr Gln Pro Tyr Phe Phe Asn Lys Gln Pro Thr  
 145 150 155 160

Glu Leu Asp Ala Leu Val Phe Gly His Leu Tyr Thr Ile Leu Thr Thr  
 165 170 175

Gln Leu Thr Asn Asp Glu Leu Ser Glu Lys Val Lys Asn Tyr Ser Asn  
 180 185 190

Leu Leu Ala Phe Cys Arg Arg Ile Glu Gln His Tyr Phe Glu Asp Arg  
 195 200 205

Gly Lys Gly Arg Leu Ser  
 210

&lt;210&gt; 966

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 966

Met Cys Asn Leu Pro Ile Lys Val Val Cys Arg Ala Asn Ala Glu Tyr  
 1 5 10 15

Met Ser Pro Ser Gly Lys Val Pro Xaa Xaa His Val Gly Asn Gln Val  
 20 25 30

Val Ser Glu Leu Gly Pro Ile Val Gln Phe Val Lys  
 35 40

&lt;210&gt; 967

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 967

Phe Val Lys Ala Lys Gly His Ser Leu Ser Asp Gly Leu Glu Glu Val  
 1 5 10 15

Gln Lys Ala Glu Met Lys Ala Tyr Met Glu Leu Val Asn Asn Met Leu  
 20 25 30

Leu Thr Ala Glu Leu Tyr Leu Gln Trp Cys Asp Glu  
 35 40

492

<210> 968  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (11)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (26)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 968  
 Leu Gln Trp Cys Asp Glu Ala Thr Val Gly Xaa Ile Thr His Xaa Arg  
   1                  5                  10                  15  
 Tyr Gly Ser Pro Tyr Pro Trp Pro Leu Xaa His Ile Leu Ala Tyr Gln  
                   20                  25                  30  
 Lys Gln Trp Glu Val Lys Arg Lys Xaa Lys Ala Ile Gly Trp Gly Lys  
           35                  40                  45  
 Lys Thr Leu  
           50

<210> 969  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<400> 969  
 Asp Gln Val Leu Glu Asp Val Asp Gln Cys Cys Gln Ala Leu Ser Gln  
   1                  5                  10                  15  
 Arg Leu Gly Thr Gln Pro Tyr Phe Phe Asn Lys Gln Pro Thr Glu Leu  
           20                  25                  30  
 Asp Ala Leu Val Phe Gly His Leu Tyr Thr Ile  
           35                  40

<210> 970  
 <211> 41

493

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 970

Leu Thr Thr Gln Leu Thr Asn Asp Glu Leu Ser Glu Lys Val Lys Asn  
 1 5 10 15

Tyr Ser Asn Leu Leu Ala Phe Cys Arg Arg Ile Glu Gln His Tyr Phe  
 20 25 30

Glu Asp Arg Gly Lys Gly Arg Leu Ser  
 35 40

&lt;210&gt; 971

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 971

Met Xaa Xaa Xaa Asn Ser His Ile Thr Ile Phe Thr Leu Asn Val Asn  
 1 5 10 15

Gly Leu Asn Ala Pro Asn Glu Arg His Arg Leu Ala Asn Trp Ile Gln  
 20 25 30

Ser Gln Asp Gln Val Cys Cys Ile Gln Glu Thr His Leu Thr Gly Arg  
 35 40 45

Asp Thr His Arg Leu Lys Ile Lys Gly Trp Arg Lys Ile Tyr Gln Ala  
 50 55 60

Asn Gly Lys Gln Lys Lys  
 65 70

&lt;210&gt; 972

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 972

Phe Thr Leu Asn Val Asn Gly Leu Asn Ala Pro Asn Glu Arg His Arg

494

1                      5                      10                      15  
 Leu Ala Asn Trp Ile Gln Ser Gln Asp Gln Val Cys  
                     20                      25

<210> 973  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 973  
 Thr His Leu Thr Gly Arg Asp Thr His Arg Leu Lys Ile Lys Gly Trp  
       1                      5                      10                      15

Arg

<210> 974  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<400> 974  
 Gly Trp Arg Lys Ile Tyr Gln Ala Asn Gly Lys Gln Lys Lys  
       1                      5                      10

<210> 975  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 975  
 Ile Tyr His Leu His Ser Trp Ile Phe Phe His Phe Lys Arg Ala Phe  
       1                      5                      10                      15

Cys Met Cys Phe Ile Thr Met Lys Val Ile His Ala His Cys Ser Lys  
                     20                      25                      30

Leu Arg Lys Cys Xaa Asn Ala Gln Ile Ser Val Phe Cys Thr Thr Leu  
                     35                      40                      45

Thr Ala Ser Tyr Pro Thr  
                     50

<210> 976  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

495

&lt;400&gt; 976

Ile Tyr His Leu His Ser Trp Ile Phe Phe His Phe Lys Arg Ala Phe  
 1 5 10 15

Cys Met Cys Phe Ile Thr Met  
 20

&lt;210&gt; 977

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 977

Lys Val Ile His Ala His Cys Ser Lys Leu Arg Lys Cys Xaa Asn Ala  
 1 5 10 15

Gln Ile Ser Val Phe Cys Thr Thr Leu Thr Ala Ser Tyr Pro Thr  
 20 25 30

&lt;210&gt; 978

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 978

Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser Ile Leu  
 1 5 10 15

Pro Gly Leu Val Leu Ala Ser Cys Asp Gly Pro Ser Xaa Ser Gln Ala  
 20 25 30

Pro Ser Pro Trp Leu Thr Pro Asp Pro Ala Ser Val Gln Val Arg Leu  
 35 40 45

Leu Trp Asp Val Leu Thr Pro Asp Pro Asn  
 50 55

&lt;210&gt; 979

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 979

Gln Arg Gly Ile Tyr Arg Glu Ile Leu Phe Leu Thr Met Ala Ala Leu  
 1 5 10 15

496

Gly Lys Asp His Val Asp Ile Val Ala Phe Asp Lys Lys Tyr Lys Ser  
                   20                  25                  30

Ala Phe Asn Lys Leu Ala Ser Ser Met Gly Lys Glu Glu Leu Arg His  
                   35                  40                  45

Arg Arg Ala Gln Met Pro  
                   50

&lt;210&gt; 980

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 980

Trp Asn Leu Leu Trp Tyr Phe Gln Arg Leu Arg Leu Pro Ser Ile Leu  
           1                  5                  10                  15

Pro Gly Leu Val Leu Ala Ser  
                   20

&lt;210&gt; 981

&lt;211&gt; 191

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 981

Glu Asp Asp Gly Phe Asn Arg Ser Ile His Glu Val Ile Leu Lys Asn  
           1                  5                  10                  15

Ile Thr Trp Tyr Ser Glu Arg Val Leu Thr Glu Ile Ser Leu Gly Ser  
                   20                  25                  30

Leu Leu Ile Leu Val Val Ile Arg Thr Ile Gln Tyr Asn Met Thr Arg  
           35                  40                  45

Thr Arg Asp Lys Tyr Leu His Thr Asn Cys Leu Ala Ala Leu Ala Asn  
           50                  55                  60

Met Ser Ala Gln Phe Arg Ser Leu His Gln Tyr Ala Ala Gln Arg Ile  
           65                  70                  75                  80

Ile Ser Leu Phe Ser Leu Leu Ser Lys Lys His Asn Lys Val Leu Glu  
                   85                  90                  95

Gln Ala Thr Gln Ser Leu Arg Gly Ser Leu Ser Ser Asn Asp Val Pro  
                   100                  105                  110

Leu Pro Asp Tyr Ala Gln Asp Leu Asn Val Ile Glu Glu Val Ile Arg  
           115                  120                  125

Met Met Leu Glu Ile Ile Asn Ser Cys Leu Thr Asn Ser Leu His His  
           130                  135                  140

Asn Pro Asn Leu Val Tyr Ala Leu Leu Tyr Lys Arg Asp Leu Phe Glu

497

145                      150                      155                      160  
 Gln Phe Arg Thr His Pro Ser Phe Gln Asp Ile Met Gln Asn Ile Asp  
                          165                      170                      175  
 Leu Val Ile Ser Phe Phe Ser Ser Arg Leu Leu Gln Ala Gly Ser  
                          180                      185                      190

<210> 982  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 982  
 Glu Asp Asp Gly Phe Asn Arg Ser Ile His Glu Val Ile Leu Lys Asn  
   1                         5                         10                         15  
 Ile Thr Trp Tyr Ser Glu Arg Val Leu Thr Glu Ile Ser Leu Gly Ser  
                          20                         25                         30  
 Leu Leu Ile Leu Val Val  
                          35

<210> 983  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<400> 983  
 Arg Thr Ile Gln Tyr Asn Met Thr Arg Thr Arg Asp Lys Tyr Leu His  
   1                         5                         10                         15  
 Thr Asn Cys Leu Ala Ala Leu Ala Asn Met Ser Ala Gln Phe Arg Ser  
                          20                         25                         30  
 Leu His Gln Tyr Ala Ala Gln Arg Ile Ile Ser Leu Phe Ser Leu Leu  
                          35                         40                         45  
 Ser Lys Lys His Asn  
                          50

<210> 984  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 984  
 Ser Cys Leu Thr Asn Ser Leu His His Asn Pro Asn Leu Val Tyr Ala  
   1                         5                         10                         15  
 Leu Leu Tyr Lys Arg Asp Leu Phe Glu Gln Phe Arg Thr His Pro Ser  
                          20                         25                         30  
 Phe Gln Asp Ile Met Gln Asn Ile Asp Leu Val Ile Ser Phe Phe Ser  
                          35                         40                         45

498

Ser Arg Leu Leu Gln Ala Gly Ser  
 50 55

&lt;210&gt; 985

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 985

Lys Lys His Asn Lys Val Leu Glu Gln Ala Thr Gln Ser Leu Arg Gly  
 1 5 10 15

Ser Leu Ser Ser Asn Asp Val Pro Leu Pro Asp Tyr Ala Gln Asp  
 20 25 30

&lt;210&gt; 986

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 986

Thr Ile Ser Asn Ser Ser Phe Ile Ser Gly Tyr Asn Ala Lys Tyr  
 1 5 10 15

&lt;210&gt; 987

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 987

Leu Lys Val Ala Ala Ser Trp Glu Leu Ser Cys Gln Trp Asn Gly Ser  
 1 5 10 15

Trp Lys Ser Leu Ser Lys Ala Ser Leu Arg Cys Pro Lys Thr Asp  
 20 25 30

&lt;210&gt; 988

&lt;211&gt; 125

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 988

Met Ala Asp Ile Gln Thr Glu Arg Ala Tyr Gln Lys Gln Pro Thr Ile  
 1 5 10 15

Phe Gln Asn Lys Lys Arg Val Leu Leu Gly Glu Thr Gly Lys Glu Lys  
 20 25 30

Leu Pro Arg Val Thr Asn Lys Asn Ile Gly Leu Gly Phe Lys Asp Thr  
 35 40 45

Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro Phe  
 50 55 60



499

Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val Thr  
 65 70 75 80  
 Gln Asp Glu Asp Ala Glu Asp His Cys His Pro Pro Arg Leu Ser Ala  
 85 90 95  
 Leu His Pro Gln Val Gln Pro Leu Arg Glu Ala Pro Gln Glu His Val  
 100 105 110  
 Cys Thr Pro Val Pro Leu Leu Gln Gly Arg Pro Asp Arg  
 115 120 125

<210> 989  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 989  
 Met Lys Met Gln Arg Thr Ile Val Ile Arg Arg Asp Tyr Leu His Tyr  
 1 5 10 15  
 Ile Arg Lys Tyr Asn Arg Phe Glu Lys Arg His Lys Asn Met Ser Val  
 20 25 30  
 His Leu Ser Pro Cys Phe Arg Asp Val Gln Ile Gly Asp Ile Val Thr  
 35 40 45  
 Val Gly Glu Cys Arg Pro Leu Ser Lys Thr Val Arg Phe Asn Val Leu  
 50 55 60  
 Lys Val Thr Lys Ala Ala Gly Thr Lys Lys Gln Phe Gln Lys Phe  
 65 70 75

<210> 990  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 990  
 Met Ala Asp Ile Gln Thr Glu Arg Ala Tyr Gln Lys Gln Pro Thr Ile  
 1 5 10 15  
 Phe Gln Asn Lys Lys Arg Val Leu Leu Gly Glu Thr Gly Lys  
 20 25 30

<210> 991  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<400> 991  
 Lys Leu Pro Arg Val Thr Asn Lys Asn Ile Gly Leu Gly Phe Lys Asp  
 1 5 10 15

500

Thr Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro  
                   20                  25                  30

Phe Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val  
                   35                  40                  45

Thr Gln Asp Glu Asp Ala Glu Asp His Cys  
           50                  55

<210> 992  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 992  
 His Cys His Pro Pro Arg Leu Ser Ala Leu His Pro Gln Val Gln Pro  
   1                  5                  10                  15

Leu Arg Glu Ala Pro Gln Glu His Val Cys Thr Pro Val Pro Leu Leu  
                   20                  25                  30

Gln Gly Arg Pro Asp Arg  
           35

<210> 993  
 <211> 36  
 <212> PRT  
 <213> Homo sapiens

<400> 993  
 Met Lys Met Gln Arg Thr Ile Val Ile Arg Arg Asp Tyr Leu His Tyr  
   1                  5                  10                  15

Ile Arg Lys Tyr Asn Arg Phe Glu Lys Arg His Lys Asn Met Ser Val  
                   20                  25                  30

His Leu Ser Pro  
           35

<210> 994  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<400> 994  
 Cys Phe Arg Asp Val Gln Ile Gly Asp Ile Val Thr Val Gly Glu Cys  
   1                  5                  10                  15

Arg Pro Leu Ser Lys Thr Val Arg Phe Asn Val Leu Lys Val Thr Lys  
                   20                  25                  30

Ala Ala Gly Thr Lys Lys Gln Phe Gln Lys Phe  
           35                  40

501

<210> 995  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 995  
 Pro Arg Arg Leu Leu Arg Gly Thr Tyr Ile Asp Lys Lys Cys Pro Phe  
 1 5 10 15

Thr Gly Asn Val Ser Ile Arg Gly Arg Ile Leu Ser Gly Val Val Thr  
 20 25 30

Gln

<210> 996  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 996  
 Ser Arg Gly Thr Gly Val Gln Thr Cys Ser Cys Gly Ala Ser Arg Ser  
 1 5 10 15

Gly Cys Thr Cys Gly Cys Ser Ala Asp Ser Leu Gly Gly  
 20 25

<210> 997  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 997  
 Gln Trp Ser Ser Ala Ser Ser Ser Trp Val Thr Thr Pro Glu Arg Ile  
 1 5 10 15

Arg Pro Arg Met Asp Thr Leu Pro Val Lys Gly His Phe Leu Ser Met  
 20 25 30

<210> 998  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 998  
 Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met  
 1 5 10 15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg  
 20 25 30

Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln Arg Ala Lys

502

35 40 45

Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly  
 50 55 60

<210> 999  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (19)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 999  
 Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys His  
 1 5 10 15

Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg Asp  
 20 25 30

Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val Phe Leu Leu  
 35 40 45

Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala Xaa Asp Thr  
 50 55 60

Val His Phe  
 65

<210> 1000  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 1000  
 Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met  
 1 5 10 15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg  
 20 25 30

<210> 1001  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

503

&lt;400&gt; 1001

Val Tyr Arg Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln  
1 5 10 15

Arg Ala Lys Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly  
20 25 30

&lt;210&gt; 1002

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1002

Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys His  
1 5 10 15

Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg Asp  
20 25 30

Met

&lt;210&gt; 1003

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1003

Arg Arg Asp Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val  
1 5 10 15

Phe Leu Leu Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala  
20 25 30

Xaa Asp Thr Val His Phe  
35

&lt;210&gt; 1004

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1004

Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met

504

1                    5                    10                    15  
Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg  
                  20                    25                    30

Leu Ile Cys Lys Gly  
                  35

&lt;210&gt; 1005

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1005

Ile Phe Tyr Asp Ser Asp Trp Asn Pro Thr Val Asp Gln Gln Ala Met  
1                    5                    10                    15

Asp Arg Ala His Arg Leu Gly Gln Thr Lys Gln Val Thr Val Tyr Arg  
                  20                    25                    30

Leu Ile Cys Lys Gly  
                  35

&lt;210&gt; 1006

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1006

Arg Leu Ile Cys Lys Gly Thr Ile Glu Glu Arg Ile Leu Gln Arg Ala  
1                    5                    10                    15

Lys Glu Lys Ser Glu Ile Gln Arg Met Val Ile Ser Gly  
                  20                    25

&lt;210&gt; 1007

&lt;211&gt; 69

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (63)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1007

Gly Thr Arg Met Ile Asp Leu Leu Glu Glu Tyr Met Val Tyr Arg Lys  
1                    5                    10                    15

His Thr Tyr Xaa Arg Leu Asp Gly Ser Ser Lys Ile Ser Glu Arg Arg

505

20                      25                      30  
 Asp Met Val Ala Asp Phe Gln Asn Arg Asn Asp Ile Phe Val Phe Leu  
                     35                      40                      45  
 Leu Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Thr Ala Xaa Asp  
                     50                      55                      60  
 Thr Val His Phe Leu  
                     65

&lt;210&gt; 1008

&lt;211&gt; 364

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (259)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (312)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1008

Met Ser Leu His Gly Lys Arg Lys Glu Ile Tyr Lys Tyr Glu Ala Pro  
                     1                      5                      10                      15

Trp Thr Val Tyr Ala Met Asn Trp Ser Val Arg Pro Asp Lys Arg Phe  
                     20                      25                      30

Arg Leu Ala Leu Gly Ser Phe Val Glu Glu Tyr Asn Asn Lys Val Gln  
                     35                      40                      45

Leu Val Gly Leu Asp Glu Glu Ser Ser Glu Phe Ile Cys Arg Asn Thr  
                     50                      55                      60

Phe Asp His Pro Tyr Pro Thr Thr Lys Leu Met Trp Ile Pro Asp Thr  
                     65                      70                      75                      80

Lys Gly Val Tyr Pro Asp Leu Leu Ala Thr Ser Gly Asp Tyr Leu Arg  
                     85                      90                      95

Val Trp Arg Val Gly Glu Thr Glu Thr Arg Leu Glu Cys Leu Leu Asn  
                     100                      105                      110

Asn Asn Lys Asn Ser Asp Phe Cys Ala Pro Leu Thr Ser Phe Asp Trp  
                     115                      120                      125

Asn Glu Val Asp Pro Tyr Leu Leu Gly Thr Ser Ser Ile Asp Thr Thr  
                     130                      135                      140

Cys Thr Ile Trp Gly Leu Glu Thr Gly Gln Val Leu Gly Arg Val Asn  
                     145                      150                      155                      160

506

Leu Val Ser Gly His Val Lys Thr Gln Leu Ile Ala His Asp Lys Glu  
                                   165                                  170                                  175  
 Val Tyr Asp Ile Ala Phe Ser Arg Ala Gly Gly Gly Arg Asp Met Phe  
                                   180                                  185                                  190  
 Ala Ser Val Gly Ala Asp Gly Ser Val Arg Met Phe Asp Leu Arg His  
                                   195                                  200                                  205  
 Leu Glu His Ser Thr Ile Ile Tyr Glu Asp Pro Gln His His Pro Leu  
                                   210                                  215                                  220  
 Leu Arg Leu Cys Trp Asn Lys Gln Asp Pro Asn Tyr Leu Ala Thr Met  
                                   225                                  230                                  235                                  240  
 Ala Met Asp Gly Met Glu Val Val Ile Leu Asp Val Arg Val Pro Ala  
                                   245                                  250                                  255  
 His Leu Xaa Pro Gly Thr Thr Ile Glu His Val Ser Met Ala Leu Leu  
                                   260                                  265                                  270  
 Gly Pro His Ile His Pro Ala Thr Ser Ala Leu Gln Arg Met Thr Thr  
                                   275                                  280                                  285  
 Arg Leu Ser Ser Gly Thr Ser Ser Lys Cys Pro Glu Pro Leu Arg Thr  
                                   290                                  295                                  300  
 Leu Ser Trp Pro Thr Gln Leu Xaa Gly Glu Ile Asn Asn Val Gln Trp  
                                   305                                  310                                  315                                  320  
 Ala Ser Thr Gln Pro Glu Leu Ser Pro Ser Ala Thr Thr Thr Ala Trp  
                                   325                                  330                                  335  
 Arg Tyr Ser Glu Cys Ser Val Gly Gly Ala Val Pro Thr Arg Gln Gly  
                                   340                                  345                                  350  
 Leu Leu Tyr Phe Leu Pro Leu Pro His Pro Gln Ser  
                                   355                                  360

&lt;210&gt; 1009

&lt;211&gt; 136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1009

Met Ser Leu His Gly Lys Arg Lys Glu Ile Tyr Lys Tyr Glu Ala Pro  
   1                                  5                                  10                                  15  
 Trp Thr Val Tyr Ala Met Asn Trp Ser Val Arg Pro Asp Lys Arg Phe  
                                   20                                  25                                  30  
 Arg Leu Ala Leu Gly Ser Phe Val Glu Glu Tyr Asn Asn Lys Val Gln  
                                   35                                  40                                  45  
 Leu Val Gly Leu Asp Glu Glu Ser Ser Glu Phe Ile Cys Arg Asn Thr  
                                   50                                  55                                  60



507

Phe Asp His Pro Tyr Pro Thr Thr Lys Leu Met Trp Ile Pro Asp Thr  
65 70 75 80

Lys Gly Val Tyr Pro Asp Leu Leu Ala Thr Ser Gly Asp Tyr Leu Arg  
85 90 95

Val Trp Arg Val Gly Glu Thr Glu Thr Arg Leu Glu Cys Leu Leu Asn  
100 105 110

Asn Asn Lys Asn Ser Asp Phe Cys Ala Pro Leu Thr Ser Phe Asp Trp  
115 120 125

Asn Glu Val Asp Pro Tyr Leu Leu  
130 135

&lt;210&gt; 1010

&lt;211&gt; 140

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (135)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1010

Ser Phe Asp Trp Asn Glu Val Asp Pro Tyr Leu Leu Gly Thr Ser Ser  
1 5 10 15

Ile Asp Thr Thr Cys Thr Ile Trp Gly Leu Glu Thr Gly Gln Val Leu  
20 25 30

Gly Arg Val Asn Leu Val Ser Gly His Val Lys Thr Gln Leu Ile Ala  
35 40 45

His Asp Lys Glu Val Tyr Asp Ile Ala Phe Ser Arg Ala Gly Gly Gly  
50 55 60

Arg Asp Met Phe Ala Ser Val Gly Ala Asp Gly Ser Val Arg Met Phe  
65 70 75 80

Asp Leu Arg His Leu Glu His Ser Thr Ile Ile Tyr Glu Asp Pro Gln  
85 90 95

His His Pro Leu Leu Arg Leu Cys Trp Asn Lys Gln Asp Pro Asn Tyr  
100 105 110

Leu Ala Thr Met Ala Met Asp Gly Met Glu Val Val Ile Leu Asp Val  
115 120 125

Arg Val Pro Ala His Leu Xaa Pro Gly Thr Thr Ile  
130 135 140

&lt;210&gt; 1011

&lt;211&gt; 170

&lt;212&gt; PRT

508

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (118)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1011

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gly | Ala | Asp | Gly | Ser | Val | Arg | Met | Phe | Asp | Leu | Arg | His | Leu | Glu |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ser | Thr | Ile | Ile | Tyr | Glu | Asp | Pro | Gln | His | His | Pro | Leu | Leu | Arg |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Cys | Trp | Asn | Lys | Gln | Asp | Pro | Asn | Tyr | Leu | Ala | Thr | Met | Ala | Met |
|     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Gly | Met | Glu | Val | Val | Ile | Leu | Asp | Val | Arg | Val | Pro | Ala | His | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Pro | Gly | Thr | Thr | Ile | Glu | His | Val | Ser | Met | Ala | Leu | Leu | Gly | Pro |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ile | His | Pro | Ala | Thr | Ser | Ala | Leu | Gln | Arg | Met | Thr | Thr | Arg | Leu |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Gly | Thr | Ser | Ser | Lys | Cys | Pro | Glu | Pro | Leu | Arg | Thr | Leu | Ser |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Pro | Thr | Gln | Leu | Xaa | Gly | Glu | Ile | Asn | Asn | Val | Gln | Trp | Ala | Ser |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gln | Pro | Glu | Leu | Ser | Pro | Ser | Ala | Thr | Thr | Thr | Ala | Trp | Arg | Tyr |
|     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Cys | Ser | Val | Gly | Gly | Ala | Val | Pro | Thr | Arg | Gln | Gly | Leu | Leu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |

|     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Phe | Leu | Pro | Leu | Pro | His | Pro | Gln | Ser |
|     |     |     | 165 |     |     |     |     | 170 |     |

&lt;210&gt; 1012

&lt;211&gt; 286

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

509

&lt;221&gt; SITE

&lt;222&gt; (258)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1012

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Leu Tyr Ala Thr Ala Thr Val Ile Ser Ser Pro Ser Thr Glu Xaa Leu
 1              5              10              15

Ser Gln Asp Gln Gly Asp Arg Ala Ser Leu Asp Ala Ala Asp Ser Gly
          20              25              30

Arg Gly Ser Trp Thr Ser Cys Ser Ser Gly Ser His Asp Asn Ile Gln
      35              40              45

Thr Ile Gln His Gln Arg Ser Trp Glu Thr Leu Pro Phe Gly His Thr
 50              55              60

His Phe Asp Tyr Ser Gly Asp Pro Ala Gly Leu Trp Ala Ser Ser Ser
 65              70              75              80

His Met Asp Gln Ile Met Phe Ser Asp His Ser Thr Lys Tyr Asn Arg
          85              90              95

Gln Asn Gln Ser Arg Glu Ser Leu Glu Gln Ala Gln Ser Arg Ala Ser
      100              105              110

Trp Ala Ser Ser Thr Gly Tyr Trp Gly Glu Asp Ser Glu Gly Asp Thr
      115              120              125

Gly Thr Ile Lys Arg Arg Gly Gly Lys Asp Val Ser Ile Glu Ala Glu
 130              135              140

Ser Ser Ser Leu Thr Ser Val Thr Thr Glu Glu Thr Lys Pro Val Pro
 145              150              155              160

Met Pro Ala His Ile Ala Val Ala Ser Ser Thr Thr Lys Gly Leu Ile
          165              170              175

Ala Arg Lys Glu Gly Arg Tyr Arg Glu Pro Pro Pro Thr Pro Pro Gly
      180              185              190

Tyr Ile Gly Ile Pro Ile Thr Asp Phe Pro Glu Gly His Ser His Pro
 195              200              205

Ala Arg Lys Pro Pro Asp Tyr Asn Val Ala Leu Gln Arg Ser Arg Met
 210              215              220

Val Ala Arg Ser Ser Asp Thr Ala Gly Pro Ser Ser Val Gln Gln Pro
 225              230              235              240

His Gly His Pro Thr Ser Ser Arg Pro Val Asn Lys Pro Gln Trp His
          245              250              255

Lys Xaa Asn Glu Ser Asp Pro Arg Leu Ala Pro Tyr Gln Ser Gln Gly
      260              265              270

Phe Ser Thr Glu Glu Asp Glu Asp Glu Gln Val Ser Ala Val
      275              280              285

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510

&lt;210&gt; 1013

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1013

His Met Asp Gln Ile Met Phe Ser Asp His Ser Thr Lys Tyr Asn Arg  
 1 5 10 15

Gln Asn Gln Ser Arg Glu Ser Leu Glu Gln Ala Gln Ser Arg Ala Ser  
 20 25 30

Trp Ala Ser Ser Thr Gly Tyr Trp Gly Glu  
 35 40

&lt;210&gt; 1014

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1014

Ser Val Thr Thr Glu Glu Thr Lys Pro Val Pro Met Pro Ala His Ile  
 1 5 10 15

Ala Val Ala Ser Ser Thr Thr Lys Gly Leu Ile Ala Arg Lys Glu Gly  
 20 25 30

Arg Tyr Arg Glu Pro Pro Pro Thr Pro Pro Gly Tyr Ile Gly Ile Pro  
 35 40 45

Ile Thr Asp  
 50

&lt;210&gt; 1015

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1015

Val Ala Leu Gln Arg Ser Arg Met Val Ala Arg Ser Ser Asp Thr Ala  
 1 5 10 15

Gly Pro Ser Ser Val Gln Gln Pro His Gly His Pro Thr Ser Ser Arg  
 20 25 30

Pro Val Asn Lys Pro Gln Trp His Lys Xaa Asn Glu Ser Asp Pro Arg  
 35 40 45

Leu Ala Pro Tyr Gln Ser Gln Gly Phe

511

50

55

&lt;210&gt; 1016

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1016

Cys Leu Leu Phe Val Phe Val Ser Leu Gly Met Arg Cys Leu Phe Trp  
 1 5 10 15

Thr Ile Val Tyr Asn Val Leu Tyr Leu Lys His Lys Cys Asn Thr Val  
 20 25 30

Leu Leu Cys Tyr His Leu Cys Ser Ile  
 35 40

&lt;210&gt; 1017

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1017

Ala Cys Ser Lys Leu Ile Pro Ala Phe Glu Met Val Met Arg Ala Lys  
 1 5 10 15

Asp Asn Val Tyr His Leu Asp Cys Phe Ala Cys Gln Leu Cys Asn Gln  
 20 25 30

Arg Xaa Cys Val Gly Asp Lys Phe Phe Leu Lys Asn Asn Xaa Xaa Leu  
 35 40 45

Cys Gln Thr Asp Tyr Glu Glu Gly Leu Met Lys Glu Gly Tyr Ala Pro  
 50 55 60

Xaa Val Arg

512

65

&lt;210&gt; 1018

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1018

Ser Ala Leu Ser Glu Pro Gly Ala Pro Asp Arg Arg Arg Pro Cys Pro  
 1 5 10 15

Glu Ser Val Pro Arg Arg Pro Asp Asp Glu Gln Trp Pro Pro Pro Thr  
 20 25 30

Ala Leu Cys Leu Asp Val Ala Pro Leu Pro Pro Ser Ser  
 35 40 45

&lt;210&gt; 1019

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1019

Pro Val Gly Tyr Leu Asp Lys Gln Val Pro Asp Thr Ser Val Gln Glu  
 1 5 10 15

Thr Asp Arg Ile Leu Val Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly  
 20 25 30

Pro Leu Lys Gln Ile Pro Met Asn Leu Phe Ile  
 35 40

&lt;210&gt; 1020

&lt;211&gt; 214

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1020

Ala His Ala Ser Glu Ser Gly Glu Arg Trp Trp Ala Cys Cys Gly Val  
 1 5 10 15

Arg Phe Gly Leu Arg Ser Ile Glu Ala Ile Gly Arg Ser Cys Cys His  
 20 25 30

Asp Gly Pro Gly Gly Leu Val Ala Asn Arg Gly Arg Arg Phe Lys Trp  
 35 40 45

Ala Ile Glu Leu Ser Gly Pro Gly Gly Gly Ser Arg Gly Arg Ser Asp  
 50 55 60

Arg Gly Ser Gly Gln Gly Asp Ser Leu Tyr Pro Val Gly Tyr Leu Asp  
 65 70 75 80

Lys Gln Val Pro Asp Thr Ser Val Gln Glu Thr Asp Arg Ile Leu Val  
 85 90 95

513

Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly Pro Leu Lys Gln Ile Pro  
                   100                  105                  110  
 Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe  
                   115                  120                  125  
 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu  
                   130                  135                  140  
 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys  
                   145                  150                  155                  160  
 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala  
                   165                  170                  175  
 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala  
                   180                  185                  190  
 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Phe Ser  
                   195                  200                  205  
 Gly Gly Gly Leu Leu Leu  
                   210

<210> 1021  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 1021  
 Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys Phe Leu Gln Gly  
   1                  5                  10                  15  
 Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala Leu Ala Val Tyr  
                   20                  25                  30  
 Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala Ser Asp  
                   35                  40                  45

<210> 1022  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<400> 1022  
 Pro Val Gly Tyr Leu Asp Lys Gln Val Pro Asp Thr Ser Val Gln Glu  
   1                  5                  10                  15  
 Thr Asp Arg Ile Leu Val Glu Lys Arg Cys Trp Asp Ile Ala Leu Gly  
                   20                  25                  30  
 Pro Leu Lys Gln Ile Pro Met Asn Leu Phe Ile  
                   35                  40

514

&lt;210&gt; 1023

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1023

Pro Thr Thr Lys Leu Asp Ile Met Glu Lys Lys Lys His Ile Gln Ile  
 1 5 10 15

Arg Phe Pro Ser Phe Tyr His Lys Leu Val Asp Ser Gly Arg Met Arg  
 20 25 30

Ser Lys Arg Glu Thr Arg Arg Glu Asp Ser Asp Thr Lys His Asn Leu  
 35 40 45

&lt;210&gt; 1024

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1024

Phe Leu Trp Lys Ser Leu Leu Leu Arg Tyr Phe Lys Met Arg Gln His  
 1 5 10 15

&lt;210&gt; 1025

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1025

Tyr His Tyr Leu Leu Ser Ser Phe Leu Ser Tyr Ser Ser Ser Ser Gln  
 1 5 10 15

Asn Leu Pro Val Tyr Gly Arg Lys Met Gly Thr Leu Phe Glu Cys Val  
 20 25 30

Phe Phe Phe Pro  
 35

&lt;210&gt; 1026

&lt;211&gt; 167

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1026

Thr Glu His Ile Ile Ala Val Met Ile Thr Glu Leu Arg Gly Lys Asp  
 1 5 10 15

Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val Gln Met Thr Ile Ala



515

|   |     |         |
|---|-----|---------|
| 20  | 25  | 30      |
| Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser Arg Gly Ser Leu Val |     |         |
| 35  | 40  | 45      |
| Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp |     |         |
| 50  | 55  | 60      |
| Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr Thr Asn Ala Arg Asp |     |         |
| 65  | 70  | 75 80   |
| Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys Lys Ala Ile Ser Lys |     |         |
| 85  | 90  | 95      |
| Leu Thr Thr Arg Thr Val Lys Lys Gly Asp Lys Glu Thr Asp Pro Asp |     |         |
| 100   | 105 | 110     |
| Phe Asp His Cys Ala Val Cys Ile Glu Ser Tyr Lys Gln Asn Asp Val |     |         |
| 115   | 120 | 125     |
| Val Arg Ile Leu Pro Cys Lys His Val Phe His Lys Ser Cys Val Asp |     |         |
| 130   | 135 | 140     |
| Pro Trp Leu Ser Glu His Cys Thr Cys Pro Met Cys Lys Leu Asn Ile |     |         |
| 145   | 150 | 155 160 |
| Leu Lys Ala Leu Gly Ile Val                                     |     |         |
| 165   |     |         |

&lt;210&gt; 1027

&lt;211&gt; 276

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1027

|   |     |       |
|---|-----|-------|
| Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr Glu |     |       |
| 1   | 5   | 10 15 |
| Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val |     |       |
| 20  | 25  | 30    |
| Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser |     |       |
| 35  | 40  | 45    |
| Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile |     |       |
| 50  | 55  | 60    |
| Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr |     |       |
| 65  | 70  | 75 80 |
| Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys |     |       |
| 85  | 90  | 95    |
| Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys Gly Asp Lys |     |       |
| 100   | 105 | 110   |
| Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile Glu Ser Tyr |     |       |

516

| 115  | 120 | 125 |
|--|-----|-----|
| Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His Val Phe His<br>130 135 140     |     |     |
| Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr Cys Pro Met<br>145 150 155 160 |     |     |
| Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro Asn Leu Pro<br>165 170 175     |     |     |
| Cys Thr Asp Asn Val Ala Phe Asp Met Glu Arg Leu Thr Arg Thr Gln<br>180 185 190     |     |     |
| Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp Asn Ser<br>195 200 205     |     |     |
| Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu Pro Gln<br>210 215 220     |     |     |
| Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala Val Thr<br>225 230 235 240 |     |     |
| Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala Leu Thr<br>245 250 255     |     |     |
| Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala Asn Glu<br>260 265 270     |     |     |
| Val Glu Trp Phe<br>275   |     |     |

<210> 1028  
 <211> 69  
 <212> PRT  
 <213> Homo sapiens

<400> 1028  
 Thr Glu His Ile Ile Ala Val Met Ile Thr Glu Leu Arg Gly Lys Asp  
 1 5 10 15  
 Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val Gln Met Thr Ile Ala  
 20 25 30  
 Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser Arg Gly Ser Leu Val  
 35 40 45  
 Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp  
 50 55 60  
 Leu Ile Phe Tyr Phe  
 65

<210> 1029  
 <211> 58  
 <212> PRT

517

&lt;213&gt; Homo sapiens

&lt;400&gt; 1029

```

Ser Ile Ser Phe Ile Val Leu Met Ile Ile Ser Ser Ala Trp Leu Ile
 1             5             10             15

Phe Tyr Phe Ile Gln Lys Ile Arg Tyr Thr Asn Ala Arg Asp Arg Asn
          20             25             30

Gln Arg Arg Leu Gly Asp Ala Ala Lys Lys Ala Ile Ser Lys Leu Thr
          35             40             45

Thr Arg Thr Val Lys Lys Gly Asp Lys Glu
 50             55

```

&lt;210&gt; 1030

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1030

```

Val Lys Lys Gly Asp Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala
 1             5             10             15

Val Cys Ile Glu Ser Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro
          20             25             30

Cys Lys His Val Phe His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu
          35             40             45

His Cys Thr Cys Pro Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly
          50             55             60

Ile Val
 65

```

&lt;210&gt; 1031

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1031

```

Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr Glu
 1             5             10             15

Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser Val
          20             25             30

Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe Ser
          35             40             45

Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met Ile
          50             55             60

Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg Tyr
          65             70             75             80

```

518

Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala Lys  
                             85                            90                            95

Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr  
                             100                            105

&lt;210&gt; 1032

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1032

Ala Ala Lys Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys  
   1                            5                            10                            15

Gly Asp Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile  
                             20                            25                            30

Glu Ser Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His  
                             35                            40                            45

Val Phe His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr  
                             50                            55                            60

Cys Pro Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro  
   65                            70                            75                            80

Asn Leu Pro Cys

&lt;210&gt; 1033

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1033

Thr Gln Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp  
   1                            5                            10                            15

Asn Ser Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu  
                             20                            25                            30

Pro Gln Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala  
                             35                            40                            45

Val Thr Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala  
                             50                            55                            60

Leu Thr Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala  
   65                            70                            75                            80

Asn Glu Val Glu Trp Phe  
                             85

519

&lt;210&gt; 1034

&lt;211&gt; 341

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1034

```

Pro Leu His Gly Val Ala Asp His Leu Gly Cys Asp Pro Gln Thr Arg
 1              5              10              15

Phe Phe Val Pro Pro Asn Ile Lys Gln Trp Ile Ala Leu Leu Gln Arg
      20              25              30

Gly Asn Cys Thr Phe Lys Glu Lys Ile Ser Arg Ala Ala Phe His Asn
      35              40              45

Ala Val Ala Val Val Ile Tyr Asn Asn Lys Ser Lys Glu Glu Pro Val
      50              55              60

Thr Met Thr His Pro Gly Thr Glu His Ile Ile Ala Val Met Ile Thr
      65              70              75              80

Glu Leu Arg Gly Lys Asp Ile Leu Ser Tyr Leu Glu Lys Asn Ile Ser
      85              90              95

Val Gln Met Thr Ile Ala Val Gly Thr Arg Met Pro Pro Lys Asn Phe
      100              105              110

Ser Arg Gly Ser Leu Val Phe Val Ser Ile Ser Phe Ile Val Leu Met
      115              120              125

Ile Ile Ser Ser Ala Trp Leu Ile Phe Tyr Phe Ile Gln Lys Ile Arg
      130              135              140

Tyr Thr Asn Ala Arg Asp Arg Asn Gln Arg Arg Leu Gly Asp Ala Ala
      145              150              155              160

Lys Lys Ala Ile Ser Lys Leu Thr Thr Arg Thr Val Lys Lys Gly Asp
      165              170              175

Lys Glu Thr Asp Pro Asp Phe Asp His Cys Ala Val Cys Ile Glu Ser
      180              185              190

Tyr Lys Gln Asn Asp Val Val Arg Ile Leu Pro Cys Lys His Val Phe
      195              200              205

His Lys Ser Cys Val Asp Pro Trp Leu Ser Glu His Cys Thr Cys Pro
      210              215              220

Met Cys Lys Leu Asn Ile Leu Lys Ala Leu Gly Ile Val Pro Asn Leu
      225              230              235              240

Pro Cys Thr Asp Asn Val Ala Phe Asp Met Glu Arg Leu Thr Arg Thr
      245              250              255

Gln Ala Val Asn Arg Arg Ser Ala Leu Gly Asp Leu Ala Gly Asp Asn
      260              265              270

Ser Leu Gly Leu Glu Pro Leu Arg Thr Ser Gly Ile Ser Pro Leu Pro

```

520

275                      280                      285  
 Gln Asp Gly Glu Leu Thr Pro Arg Thr Gly Glu Ile Asn Ile Ala Val  
     290                      295                      300  
 Thr Lys Glu Trp Phe Ile Ile Ala Ser Phe Gly Leu Leu Ser Ala Leu  
 305                      310                      315                      320  
 Thr Leu Cys Tyr Met Ile Ile Arg Ala Thr Ala Ser Leu Asn Ala Asn  
                     325                      330                      335  
 Glu Val Glu Trp Phe  
                     340

<210> 1035  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 1035  
 His Gly Val Ala Asp His Leu Gly Cys Asp Pro Gln Thr Arg Phe Phe  
     1                      5                      10                      15  
 Val Pro Pro Asn Ile Lys Gln Trp Ile Ala Leu Leu Gln Arg Gly Asn  
                     20                      25                      30  
 Cys Thr Phe Lys Glu Lys Ile Ser Arg Ala Ala Phe His Asn Ala Val  
                     35                      40                      45  
 Ala Val Val Ile Tyr Asn Asn Lys Ser Lys Glu Glu  
                     50                      55                      60

<210> 1036  
 <211> 314  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (189)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1036  
 Met Ser Gly Gln Gly Leu Ala Gly Phe Phe Ala Ser Val Ala Met Ile  
     1                      5                      10                      15  
 Cys Ala Ile Ala Ser Gly Ser Glu Leu Ser Glu Ser Ala Phe Gly Tyr  
                     20                      25                      30  
 Phe Ile Thr Ala Cys Ala Val Ile Ile Leu Thr Ile Ile Cys Tyr Leu  
                     35                      40                      45  
 Gly Leu Pro Arg Leu Glu Phe Tyr Arg Tyr Tyr Gln Gln Leu Lys Leu  
                     50                      55                      60  
 Glu Gly Pro Gly Glu Gln Glu Thr Lys Leu Asp Leu Ile Ser Lys Gly

521

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 65  |     | 70  |     | 75  |     | 80  |     |     |     |     |     |     |     |     |     |
| Glu | Glu | Pro | Arg | Ala | Gly | Lys | Glu | Glu | Ser | Gly | Val | Ser | Val | Ser | Asn |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Ser | Gln | Pro | Thr | Asn | Glu | Ser | His | Ser | Ile | Lys | Ala | Ile | Leu | Lys | Asn |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Ile | Ser | Val | Leu | Ala | Phe | Ser | Val | Cys | Phe | Ile | Phe | Thr | Ile | Thr | Ile |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Gly | Met | Phe | Pro | Ala | Val | Thr | Val | Glu | Val | Lys | Ser | Ser | Ile | Ala | Gly |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Ser | Ser | Thr | Trp | Glu | Arg | Tyr | Phe | Ile | Pro | Val | Ser | Cys | Phe | Leu | Thr |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Phe | Asn | Ile | Phe | Asp | Trp | Leu | Gly | Arg | Ser | Leu | Thr | Ala | Val | Phe | Met |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Trp | Pro | Gly | Lys | Asp | Ser | Arg | Trp | Leu | Pro | Ser | Trp | Xaa | Leu | Ala | Arg |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Leu | Val | Phe | Val | Pro | Leu | Leu | Leu | Leu | Cys | Asn | Ile | Lys | Pro | Arg | Arg |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Tyr | Leu | Thr | Val | Val | Phe | Glu | His | Asp | Ala | Trp | Phe | Ile | Phe | Phe | Met |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Ala | Ala | Phe | Ala | Phe | Ser | Asn | Gly | Tyr | Leu | Ala | Ser | Leu | Cys | Met | Cys |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     | 240 |     |
| Phe | Gly | Pro | Lys | Lys | Val | Lys | Pro | Ala | Glu | Ala | Glu | Thr | Ala | Glu | Pro |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Trp | Pro | Ser | Ser | Cys | Val | Trp | Val | Trp | His | Trp | Gly | Leu | Phe | Ser |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Pro | Ser | Cys | Ser | Gly | Gln | Leu | Cys | Asp | Lys | Gly | Trp | Thr | Glu | Gly | Leu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Pro | Ala | Ser | Leu | Pro | Val | Cys | Leu | Leu | Pro | Leu | Pro | Ser | Ala | Arg | Gly |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Asp | Pro | Glu | Trp | Ser | Gly | Gly | Phe | Phe | Phe |     |     |     |     |     |     |
| 305 |     |     |     |     | 310 |     |     |     |     |     |     |     |     |     |     |

&lt;210&gt; 1037

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1037

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Gly | Gln | Gly | Leu | Ala | Gly | Phe | Phe | Ala | Ser | Val | Ala | Met | Ile |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Cys Ala Ile Ala Ser Gly Ser Glu Leu Ser Glu Ser Ala Phe Gly Tyr

522

20                      25                      30  
 Phe Ile Thr Ala Cys Ala Val Ile Ile Leu Thr Ile Ile Cys Tyr Leu  
           35                      40                      45  
 Gly Leu Pro Arg Leu Glu Phe Tyr Arg Tyr Tyr Gln Gln Leu Lys Leu  
           50                      55                      60  
 Glu Gly Pro Gly Glu Gln Glu Thr Lys Leu Asp Leu Ile Ser Lys Gly  
           65                      70                      75                      80  
 Glu Glu Pro Arg Ala Gly Lys Glu Glu Ser Gly Val Ser Val Ser Asn  
                           85                      90                      95  
 Ser Gln Pro Thr Asn Glu Ser His Ser Ile  
                           100                      105

<210> 1038  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 1038  
 Ser Gly Val Ser Val Ser Asn Ser Gln Pro Thr Asn Glu Ser His Ser  
   1                      5                      10                      15  
 Ile Lys Ala Ile Leu Lys Asn Ile Ser Val Leu Ala Phe Ser Val Cys  
           20                      25                      30  
 Phe Ile Phe Thr Ile Thr Ile Gly Met Phe Pro Ala Val Thr Val Glu  
           35                      40                      45  
 Val Lys Ser Ser Ile Ala Gly Ser Ser Thr Trp Glu Arg Tyr Phe Ile  
           50                      55                      60  
 Pro Val Ser Cys Phe Leu Thr Phe Asn Ile Phe Asp Trp Leu Gly Arg  
           65                      70                      75                      80  
 Ser

<210> 1039  
 <211> 92  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (63)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1039  
 Thr Ile Gly Met Phe Pro Ala Val Thr Val Glu Val Lys Ser Ser Ile  
   1                      5                      10                      15  
 Ala Gly Ser Ser Thr Trp Glu Arg Tyr Phe Ile Pro Val Ser Cys Phe



523

|   |    |  |    |  |    |    |
|---|----|--|----|--|----|----|
|   | 20 |  | 25 |  | 30 |    |
| Leu Thr Phe Asn Ile Phe Asp Trp Leu Gly Arg Ser Leu Thr Ala Val |    |  |    |  |    |    |
|   | 35 |  | 40 |  | 45 |    |
| Phe Met Trp Pro Gly Lys Asp Ser Arg Trp Leu Pro Ser Trp Xaa Leu |    |  |    |  |    |    |
|   | 50 |  | 55 |  | 60 |    |
| Ala Arg Leu Val Phe Val Pro Leu Leu Leu Leu Cys Asn Ile Lys Pro |    |  |    |  |    |    |
|   | 65 |  | 70 |  | 75 | 80 |
| Arg Arg Tyr Leu Thr Val Val Phe Glu His Asp Ala                 |    |  |    |  |    |    |
|   | 85 |  | 90 |  |    |    |

<210> 1040  
 <211> 74  
 <212> PRT  
 <213> Homo sapiens

|   |
|---|
| <400> 1040  |
| Phe Gly Pro Lys Lys Val Lys Pro Ala Glu Ala Glu Thr Ala Glu Pro |
| 1 5 10 15   |
| Ser Trp Pro Ser Ser Cys Val Trp Val Trp His Trp Gly Leu Phe Ser |
| 20 25 30  |
| Pro Ser Cys Ser Gly Gln Leu Cys Asp Lys Gly Trp Thr Glu Gly Leu |
| 35 40 45  |
| Pro Ala Ser Leu Pro Val Cys Leu Leu Pro Leu Pro Ser Ala Arg Gly |
| 50 55 60  |
| Asp Pro Glu Trp Ser Gly Gly Phe Phe Phe                         |
| 65 70   |

<210> 1041  
 <211> 135  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (96)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (97)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (98)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE  
<222> (99)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (100)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (101)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (102)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (103)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (104)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (105)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (106)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (107)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (108)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (109)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (110)  
<223> Xaa equals any of the naturally occurring L-amino acids

525

<220>  
 <221> SITE  
 <222> (111)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (112)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (130)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 1041  
 Asp Asp Asp Gly Phe Glu Ile Val Pro Ile Glu Asp Pro Ala Lys His  
   1                  5                  10                  15  
 Arg Ile Leu Asp Pro Glu Gly Leu Ala Leu Gly Ala Val Ile Ala Ser  
           20                  25                  30  
 Ser Lys Lys Ala Lys Arg Asp Leu Ile Asp Asn Ser Phe Asn Arg Tyr  
           35                  40                  45  
 Thr Phe Asn Glu Asp Glu Gly Glu Leu Pro Glu Trp Phe Val Gln Glu  
   50                  55                  60  
 Glu Lys Gln His Arg Ile Arg Gln Leu Pro Val Gly Lys Lys Glu Val  
   65                  70                  75                  80  
 Glu His Tyr Arg Lys Arg Trp Arg Glu Ile Asn Ala Arg Pro Ile Xaa  
                   85                  90                  95  
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
           100                  105                  110  
 Leu Glu Gln Thr Arg Lys Lys Ala Glu Ala Val Val Asn Thr Val Asp  
   115                  120                  125  
 Ile Xaa Arg Thr Arg Glu Ser  
   130                  135

<210> 1042  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 1042  
 Asp Asp Asp Gly Phe Glu Ile Val Pro Ile Glu Asp Pro Ala Lys His  
   1                  5                  10                  15  
 Arg Ile Leu Asp Pro Glu Gly Leu Ala Leu Gly Ala Val Ile Ala Ser  
           20                  25                  30  
 Ser Lys Lys Ala Lys Arg Asp Leu Ile Asp Asn Ser Phe Asn Arg Tyr

526

35

40

45

Thr Phe

50

&lt;210&gt; 1043

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (18)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

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<222> (21)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (24)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (25)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (26)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (46)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1043
Lys Arg Trp Arg Glu Ile Asn Ala Arg Pro Ile Xaa Xaa Xaa Xaa Xaa
 1           5           10           15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 20           25           30

Arg Lys Lys Ala Glu Ala Val Val Asn Thr Val Asp Ile Xaa Arg Thr
 35           40           45

Arg Glu Ser
 50

<210> 1044

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528

&lt;211&gt; 216

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1044

Met Ile Lys Asp Lys Gly Arg Ala Arg Thr Ala Leu Thr Ser Ser Gln  
 1 5 10 15

Pro Ala His Leu Cys Pro Glu Asn Pro Leu Leu His Leu Lys Ala Ala  
 20 25 30

Val Lys Glu Lys Lys Arg Asn Lys Lys Lys Lys Thr Ile Gly Ser Pro  
 35 40 45

Lys Arg Ile Gln Ser Pro Leu Asn Asn Lys Leu Leu Asn Ser Pro Ala  
 50 55 60

Lys Thr Leu Pro Gly Ala Cys Gly Ser Pro Gln Lys Leu Ile Asp Gly  
 65 70 75 80

Phe Leu Lys His Glu Gly Pro Pro Ala Glu Lys Pro Leu Glu Glu Leu  
 85 90 95

Ser Ala Ser Thr Ser Gly Val Pro Gly Leu Ser Ser Leu Gln Ser Asp  
 100 105 110

Pro Ala Gly Cys Val Arg Pro Pro Ala Pro Asn Leu Ala Gly Ala Val  
 115 120 125

Glu Phe Asn Asp Val Lys Thr Leu Leu Arg Glu Trp Ile Thr Thr Ile  
 130 135 140

Ser Asp Pro Met Glu Glu Asp Ile Leu Gln Val Val Lys Tyr Cys Thr  
 145 150 155 160

Asp Leu Ile Glu Glu Lys Asp Leu Glu Lys Leu Asp Leu Val Ile Lys  
 165 170 175

Tyr Met Lys Arg Leu Met Gln Gln Ser Val Glu Ser Val Trp Asn Met  
 180 185 190

Ala Phe Asp Phe Ile Leu Asp Asn Val Gln Val Val Leu Gln Gln Thr  
 195 200 205

Tyr Gly Ser Thr Leu Lys Val Thr  
 210 215

&lt;210&gt; 1045

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1045

Met Ile Lys Asp Lys Gly Arg Ala Arg Thr Ala Leu Thr Ser Ser Gln  
 1 5 10 15

Pro Ala His Leu Cys Pro Glu Asn Pro Leu Leu His Leu Lys Ala Ala

529

20 25 30

Val Lys Glu Lys Lys Arg Asn Lys Lys Lys Lys Thr Ile Gly Ser Pro  
 35 40 45

Lys Arg Ile Gln  
 50

<210> 1046  
 <211> 100  
 <212> PRT  
 <213> Homo sapiens

<400> 1046

Lys Arg Ile Gln Ser Pro Leu Asn Asn Lys Leu Leu Asn Ser Pro Ala  
 1 5 10 15

Lys Thr Leu Pro Gly Ala Cys Gly Ser Pro Gln Lys Leu Ile Asp Gly  
 20 25 30

Phe Leu Lys His Glu Gly Pro Pro Ala Glu Lys Pro Leu Glu Glu Leu  
 35 40 45

Ser Ala Ser Thr Ser Gly Val Pro Gly Leu Ser Ser Leu Gln Ser Asp  
 50 55 60

Pro Ala Gly Cys Val Arg Pro Pro Ala Pro Asn Leu Ala Gly Ala Val  
 65 70 75 80

Glu Phe Asn Asp Val Lys Thr Leu Leu Arg Glu Trp Ile Thr Thr Ile  
 85 90 95

Ser Asp Pro Met  
 100

<210> 1047  
 <211> 74  
 <212> PRT  
 <213> Homo sapiens

<400> 1047

Thr Ile Ser Asp Pro Met Glu Glu Asp Ile Leu Gln Val Val Lys Tyr  
 1 5 10 15

Cys Thr Asp Leu Ile Glu Glu Lys Asp Leu Glu Lys Leu Asp Leu Val  
 20 25 30

Ile Lys Tyr Met Lys Arg Leu Met Gln Gln Ser Val Glu Ser Val Trp  
 35 40 45

Asn Met Ala Phe Asp Phe Ile Leu Asp Asn Val Gln Val Val Leu Gln  
 50 55 60

Gln Thr Tyr Gly Ser Thr Leu Lys Val Thr  
 65 70

530

&lt;210&gt; 1048

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1048

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Cys | Cys | Lys | Thr | Thr | Trp | Thr | Leu | Ser | Arg | Ile | Lys | Ser | Asn | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Phe | Gln | Thr | Asp | Ser | Thr | Asp | Cys | Cys | Ile | Ser | Leu | Phe | Met | Tyr |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ile | Thr | Arg | Ser | Ser | Phe | Ser | Lys | Ser | Phe | Ser | Ser | Ile | Arg | Ser |
|     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Tyr | Phe | Thr | Thr | Trp | Arg | Met | Ser | Ser | Ser | Ile | Gly | Ser | Glu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Val | Val | Ile | His | Ser | Leu | Ser | Lys | Val | Phe | Thr | Ser | Leu | Asn | Ser |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ala | Pro | Ala | Arg | Leu | Gly | Ala | Gly | Gly | Leu | Thr | Gln | Pro | Ala | Gly |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Cys | Lys | Leu | Glu | Arg | Pro | Gly | Thr | Pro | Glu | Val | Glu | Ala | Glu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Ser | Arg | Gly | Phe | Ser | Ala | Gly | Gly | Pro | Ser | Cys | Phe | Arg | Asn |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ser | Ile | Asn | Phe | Trp | Gly | Leu | Pro | Gln | Ala | Pro | Gly | Arg | Val | Phe |
|     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gly | Leu | Leu | Ser | Ser | Leu | Leu | Phe | Lys | Gly | Leu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |

&lt;210&gt; 1049

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1049

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Thr | Leu | Ser | Arg | Ile | Lys | Ser | Asn | Ala | Ile | Phe | Gln | Thr | Asp | Ser |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Asp | Cys | Cys | Ile | Ser | Leu | Phe | Met |
|     | 20  |     |     |     |     |     |     | 25  |

&lt;210&gt; 1050

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1050

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Thr | Thr | Trp | Arg | Met | Ser | Ser | Ser | Ile | Gly | Ser | Glu | Ile | Val | Val |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|



531

1                    5                    10                    15  
Ile His Ser Leu Ser Lys Val Phe Thr Ser Leu Asn Ser Thr Ala Pro  
                  20                    25                    30  
Ala Arg Leu Gly Ala  
                  35

<210> 1051  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 1051  
Gly Gly Pro Ser Cys Phe Arg Asn Pro Ser Ile Asn Phe Trp Gly Leu  
1                    5                    10                    15  
Pro Gln Ala Pro Gly Arg Val Phe Ala Gly Leu Leu  
                  20                    25

<210> 1052  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 1052  
Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Asn Cys  
1                    5                    10                    15  
Glu Pro

<210> 1053  
<211> 18  
<212> PRT  
<213> Homo sapiens

<400> 1053  
Phe Cys His Asp Cys Lys Phe Pro Glu Ala Ser Pro Ala Met Asn Cys  
1                    5                    10                    15  
Glu Pro

<210> 1054  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 1054  
His Glu Pro Tyr Ala Val Leu Val Ile  
1                    5

532

&lt;210&gt; 1055

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1055

Pro Gln Pro Ser Asn Phe Pro Thr Thr Val Arg Asn Leu Pro Tyr Ser  
 1 5 10 15

Gly Ala Gly Ala Gln Pro Pro Pro Ser Asn Cys  
 20 25

&lt;210&gt; 1056

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1056

Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile  
 1 5 10 15

Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe  
 20 25 30

Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp  
 35 40 45

Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys  
 50 55 60

Ser Ala Pro Ala Cys His Ala Ser Asp Thr His Leu Leu Tyr Pro Ser  
 65 70 75 80

Thr Arg Ala Leu Cys Pro Ser Ile Phe Ala Trp Leu Val Ala Pro His  
 85 90 95

Ser Val Phe Arg Thr Asn Ala Pro Gly Pro Thr Pro Ser Ser Gln Ser  
 100 105 110

Ser Pro Val Phe Pro Val Phe Pro Val Ser Phe Met Ala Leu Ile Val  
 115 120 125

Cys Xaa Leu Val Cys Cys  
 130

&lt;210&gt; 1057

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1057

533

Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile  
 1 5 10 15

Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe  
 20 25 30

Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp  
 35 40 45

Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys  
 50 55 60

Ser Ala Pro Ala Cys His Ala  
 65 70

&lt;210&gt; 1058

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1058

Phe Ala Trp Leu Val Ala Pro His Ser Val Phe Arg Thr Asn Ala Pro  
 1 5 10 15

Gly Pro Thr Pro Ser Ser Gln Ser Ser Pro Val Phe Pro Val Phe Pro  
 20 25 30

Val Ser Phe Met Ala Leu Ile Val Cys Xaa Leu Val Cys Cys  
 35 40 45

&lt;210&gt; 1059

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1059

Met Ala Ser Ser Val Pro Ala Gly Gly His Thr Arg Ala Gly Gly Ile  
 1 5 10 15

Phe Leu Ile Gly Lys Leu Asp Leu Glu Ala Ser Leu Phe Lys Ser Phe  
 20 25 30

Gln Trp Leu Pro Phe Val Leu Arg Lys Lys Cys Asn Phe Phe Cys Trp  
 35 40 45

Asp Ser Ser Ala His Ser Leu Pro Leu His Pro Leu Ser Ala Ser Cys

534

50                      55                      60  
 Ser Ala Pro Ala Cys His Ala Ser Asp Thr His Leu Leu Tyr Pro Ser  
 65                      70                      75                      80  
 Thr Arg Ala Leu Cys Pro Ser Ile Phe Ala Trp Leu Val Ala Pro His  
                     85                      90                      95  
 Ser Val Phe Arg Thr Asn Ala Pro Gly Pro Thr Pro Ser Ser Gln Ser  
                     100                      105                      110  
 Ser Pro Val Phe Pro Val Phe Pro Val Ser Phe Met Ala Leu Ile Val  
                     115                      120                      125  
 Cys Xaa Leu Val Cys Cys  
 130

&lt;210&gt; 1060

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (112)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1060

Leu Val Asn Trp Ile Leu Lys Leu His Cys Leu Asn Leu Phe Ser Gly  
 1                      5                      10                      15  
 Phe Pro Leu Tyr Leu Glu Lys Asn Ala Thr Ser Ser Ala Gly Thr His  
                     20                      25                      30  
 Pro Leu Thr Ala Phe Pro Ser Thr Leu Ser Leu Pro His Ala Leu Pro  
                     35                      40                      45  
 Leu Pro Ala Met Pro Pro Ile Leu Thr Phe Cys Thr Pro Ala Pro Val  
                     50                      55                      60  
 Pro Ser Ala Pro Arg Ser Leu Pro Gly Trp Leu Leu Leu Thr Gln Cys  
 65                      70                      75                      80  
 Ser Gly Gln Met Leu Leu Ala Leu Pro His Leu Ala Ser Leu Ala Arg  
                     85                      90                      95  
 Ser Ser Leu Ser Ser Leu Phe His Ser Trp Leu Leu Leu Phe Val Xaa  
                     100                      105                      110  
 Leu Cys Ala Val Asp Phe  
 115

&lt;210&gt; 1061

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

535

&lt;400&gt; 1061

Asn Leu Phe Ser Gly Phe Pro Leu Tyr Leu Glu Lys Asn Ala Thr Ser  
 1 5 10 15

Ser Ala Gly Thr His Pro Leu  
 20

&lt;210&gt; 1062

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1062

Pro His Leu Ala Ser Leu Ala Arg Ser Ser Leu Ser Ser Leu Phe His  
 1 5 10 15

Ser Trp Leu Leu Leu  
 20

&lt;210&gt; 1063

&lt;211&gt; 286

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1063

Met Ala Met Glu Gly Tyr Trp Arg Phe Leu Ala Leu Leu Gly Ser Ala  
 1 5 10 15

Leu Leu Val Gly Phe Leu Ser Val Ile Phe Ala Leu Val Trp Val Leu  
 20 25 30

His Tyr Arg Glu Gly Leu Gly Trp Asp Gly Ser Ala Leu Glu Phe Asn  
 35 40 45

Trp His Pro Val Leu Met Val Thr Gly Phe Val Phe Ile Gln Gly Ile  
 50 55 60

Ala Ile Ile Val Tyr Arg Leu Pro Trp Thr Trp Lys Cys Ser Lys Leu  
 65 70 75 80

Leu Met Lys Ser Ile His Ala Gly Leu Asn Ala Val Ala Ala Ile Leu  
 85 90 95

Ala Ile Ile Ser Val Val Ala Val Phe Glu Asn His Asn Val Asn Asn  
 100 105 110

Ile Ala Asn Met Tyr Ser Leu His Ser Trp Val Gly Leu Ile Ala Val  
 115 120 125

Ile Cys Tyr Leu Leu Gln Leu Leu Ser Gly Phe Ser Val Phe Leu Leu  
 130 135 140

Pro Trp Ala Pro Leu Ser Leu Arg Ala Phe Leu Met Pro Ile His Val  
 145 150 155 160

536

Tyr Ser Gly Ile Val Ile Phe Gly Thr Val Ile Ala Thr Ala Leu Met  
 165 170 175  
 Gly Leu Thr Glu Lys Leu Ile Phe Ser Leu Arg Asp Pro Ala Tyr Ser  
 180 185 190  
 Thr Phe Pro Pro Glu Gly Val Phe Val Asn Thr Leu Gly Leu Leu Ile  
 195 200 205  
 Leu Val Phe Gly Ala Leu Ile Phe Trp Ile Val Thr Arg Pro Gln Trp  
 210 215 220  
 Lys Arg Pro Lys Glu Pro Asn Ser Thr Ile Leu His Pro Asn Gly Gly  
 225 230 235 240  
 Thr Glu Gln Gly Ala Arg Gly Ser Met Pro Ala Tyr Ser Gly Asn Asn  
 245 250 255  
 Met Asp Lys Ser Asp Ser Glu Leu Asn Ser Glu Val Ala Ala Arg Lys  
 260 265 270  
 Arg Asn Leu Ala Leu Asp Glu Ala Gly Gln Arg Ser Thr Met  
 275 280 285

<210> 1064  
 <211> 16  
 <212> PRT  
 <213> Homo sapiens

<400> 1064  
 Ala His Ala Ser Ala His Ala Ser Gly Gly Ala Glu Tyr Gly Ala Leu  
 1 5 10 15

<210> 1065  
 <211> 116  
 <212> PRT  
 <213> Homo sapiens

<400> 1065  
 Gln Tyr Ser Gln Tyr Val Gln Ser Ala Gln Leu Gly Trp Thr Asp Ser  
 1 5 10 15  
 Cys His Met Leu Phe Val Thr Ala Ser Phe Arg Phe Phe Ser Leu Ser  
 20 25 30  
 Ala Ser Met Gly Ser Ala Phe Ser Pro Ser Ile Ser His Ala His Thr  
 35 40 45  
 Cys Leu Phe Trp Asn Cys His Leu Trp Asn Ser Asp Cys Asn Ser Thr  
 50 55 60  
 Tyr Gly Ile Asp Arg Glu Thr Asp Phe Phe Pro Glu Arg Ser Cys Ile  
 65 70 75 80

.537

Gln Tyr Ile Pro Ala Arg Arg Cys Phe Arg Lys Tyr Ala Trp Pro Ser  
85 90 95

Asp Pro Gly Val Arg Gly Pro His Phe Leu Asp Ser His Gln Thr Ala  
100 105 110

Met Glu Thr Ser  
115

&lt;210&gt; 1066

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1066

Ala Ser Met Gly Ser Ala Phe Ser Pro Ser Ile Ser His Ala His Thr  
1 5 10 15

Cys Leu Phe Trp Asn Cys His Leu Trp Asn Ser Asp Cys Asn Ser Thr  
20 25 30

Tyr Gly

&lt;210&gt; 1067

&lt;211&gt; 119

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1067

Phe Val His Val Val Ala Arg Val Gly Trp His Gly Thr Ser Cys Ser  
1 5 10 15

Leu Phe Ser Ala Ser Ile Trp Met Lys Asn Gly Arg Ile Trp Leu Leu  
20 25 30

Arg Thr Phe Pro Leu Arg Ser Gly Asp Tyr Pro Lys Asn Glu Gly Pro  
35 40 45

Glu His Gln Asp Gln Lys Ala Lys Arg Ile Tyr Glu Asn Thr Phe Trp  
50 55 60

Arg Glu Cys Thr Val Cys Arg Ile Ser Gln Gly Lys Asn Gln Phe Leu  
65 70 75 80

Cys Gln Ser His Lys Cys Cys Cys Asn His Cys Ser Lys Asp Asp Asn  
85 90 95

Ser Arg Ile Asn Met Tyr Gly His Glu Lys Cys Ser Glu Arg Lys Arg  
100 105 110

Ser Pro Trp Lys Gln Lys Asp  
115

538

&lt;210&gt; 1068

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1068

Ala Ser Ile Trp Met Lys Asn Gly Arg Ile Trp Leu Leu Arg Thr Phe  
1 5 10 15

Pro Leu Arg Ser Gly Asp Tyr Pro Lys Asn Glu Gly Pro Glu His Gln  
20 25 30

&lt;210&gt; 1069

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1069

Pro Gly Arg Ala Gly Pro Ser Pro Gly Leu Ser Leu Gln Leu Pro Ala  
1 5 10 15

Glu Pro Gly His Pro Ala Gly Asn Leu Ala Pro Leu Thr Ser Arg Pro  
20 25 30

Gln Pro Leu Cys Arg Ile Pro Ala Val Pro Gly  
35 40

&lt;210&gt; 1070

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1070

Ala Arg Gly Arg Arg Gly Arg Leu Glu Leu Trp Glu Leu Cys Leu  
1 5 10 15

Pro Leu Gly Cys Arg Arg Arg Arg Ser Leu Thr Met Ala Pro Gln Ser  
20 25 30

Leu Pro Ser Ser Arg Met Ala Pro Leu Gly  
35 40

&lt;210&gt; 1071

&lt;211&gt; 351

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1071

Asn Gly Gln Ala Ser Thr Ala Lys Met Ser Ser Cys Leu Arg Ser Pro  
1 5 10 15

Pro Thr Leu Ala Pro Leu Ser Leu Thr Ser Gly Ile Pro Val Gln Ser



20

25

30

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Trp | Cys | Gly | Ala | Ser | Ser | Gln | Leu | Leu | Gln | Gln | Ala | Val | Asp | Arg | Ala |    |
|     |     |     | 35  |     |     |     |     |     | 40  |     |     |     |     |     |     | 45 |
| Gln | Gln | Leu | Leu | Glu | Val | Ala | Leu | Val | Leu | Thr | Ile | Leu | Gln | Leu | Gln |    |
|     |     | 50  |     |     |     | 55  |     |     |     |     |     | 60  |     |     |     |    |
| Ala | Gly | Gln | His | Leu | Val | Leu | Ser | Leu | Gln | Ala | Gly | Gln | Cys | Pro | Ala |    |
|     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     |     | 80 |
| Glu | Leu | Gly | Val | Leu | Thr | Val | Ala | Val | Pro | Ala | Gly | Gly | Gln | Glu | Asp |    |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     | 95  |    |
| Ala | Gln | Cys | Leu | Gln | His | Leu | Leu | Thr | Gly | Ile | Met | Leu | Gly | Gln | Arg |    |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |    |
| Gln | Glu | Val | Gly | Arg | Asp | Leu | Ala | Pro | Ala | Leu | Phe | Pro | Gln | Ala | Trp |    |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |    |
| Gln | Glu | Val | Tyr | Leu | Ala | Ile | Leu | Leu | Gln | Leu | Leu | Trp | Gly | His | Leu |    |
|     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |    |
| Leu | Gly | Gln | Leu | Ser | Leu | Leu | Leu | Gly | Glu | His | Leu | Leu | Arg | Asp | Gln |    |
|     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |    |
| Val | Val | Glu | Gln | Cys | Asp | His | Ala | His | Gly | Glu | His | Leu | Arg | Ala | Leu |    |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |    |
| Leu | Leu | His | Gln | Gly | Pro | Gln | Asp | Leu | Gln | Pro | Pro | Glu | Leu | Gln | Glu |    |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |    |
| Leu | Pro | Leu | Gly | Ile | Gly | Glu | Val | Ala | Gln | Gln | Gly | Ala | Gln | Cys | Lys |    |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |    |
| Gln | Asp | Leu | Leu | Leu | Cys | Ser | Glu | Arg | Leu | Leu | Arg | Gly | Gln | Asp | Asp |    |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |    |
| Gln | Gln | Leu | Leu | Gln | Gly | Ser | Pro | Phe | Asp | Gly | Leu | His | Leu | Asp | Leu |    |
|     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |    |
| Gly | Val | Ala | Gly | Lys | Gly | Ser | Ala | Gln | His | Lys | Arg | Ser | Ile | Leu | Leu |    |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |    |
| His | Glu | Gly | Leu | Cys | Ala | Val | Gln | Pro | Ile | Asp | His | His | Leu | Lys | Thr |    |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |    |
| Thr | Lys | Gly | Lys | Gln | Val | Leu | Arg | Ile | Val | His | Leu | Met | Asp | Ile | Ile |    |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |    |
| Phe | Lys | Ile | Lys | Glu | Arg | Ser | Asn | Leu | Leu | Phe | Gln | Thr | Gly | Ala | Gly |    |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |    |
| Thr | Ile | Glu | Leu | Val | Asp | Gln | Pro | Tyr | His | Asp | Leu | His | Val | Ser | Leu |    |
|     | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |    |
| Asn | Asp | Asn | Ile | Gln | Leu | Ile | Lys | Val | Phe | Leu | Gln | Phe | Leu | Asn | Gly |    |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     |     | 335 |    |

540

Ala Glu Glu Pro Leu Tyr Leu Ser Leu Pro Cys Leu Val Phe Leu  
340 345 350

&lt;210&gt; 1072

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1072

Gln His Leu Val Leu Ser Leu Gln Ala Gly Gln Cys Pro Ala Glu Leu  
1 5 10 15

Gly Val Leu Thr Val Ala Val Pro Ala Gly Gly Gln Glu Asp Ala Gln  
20 25 30

Cys

&lt;210&gt; 1073

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1073

Gln Leu Ser Leu Leu Leu Gly Glu His Leu Leu Arg Asp Gln Val Val  
1 5 10 15

Glu Gln Cys Asp His Ala His Gly Glu His  
20 25

&lt;210&gt; 1074

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1074

Gly Ser Pro Phe Asp Gly Leu His Leu Asp Leu Gly Val Ala Gly Lys  
1 5 10 15

Gly Ser Ala Gln His Lys Arg Ser Ile Leu Leu His Glu Gly Leu Cys  
20 25 30

&lt;210&gt; 1075

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1075

His Leu Met Asp Ile Ile Phe Lys Ile Lys Glu Arg Ser Asn Leu Leu  
1 5 10 15

541

Phe Gln Thr Gly Ala Gly Thr Ile Glu Leu Val Asp Gln Pro  
                   20                  25                  30

&lt;210&gt; 1076

&lt;211&gt; 126

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1076

Asp Glu Pro Cys Pro Pro Pro Ala Ala Ser Cys Ala Pro Pro Ser Trp  
   1                  5                  10                  15

Arg Met Glu Leu Arg Thr Gly Ser Val Gly Ser Gln Ala Val Ala Arg  
                   20                  25                  30

Arg Met Asp Gly Asp Ser Arg Asp Gly Gly Gly Gly Lys Asp Ala Thr  
                   35                  40                  45

Gly Ser Glu Asp Tyr Glu Asn Leu Pro Thr Ser Ala Ser Val Ser Thr  
   50                  55                  60

His Met Thr Ala Gly Ala Met Ala Gly Ile Leu Glu His Ser Val Met  
   65                  70                  75                  80

Tyr Pro Val Asp Ser Val Lys Thr Arg Met Gln Ser Leu Ser Pro Asp  
                   85                  90                  95

Pro Lys Ala Gln Tyr Thr Ser Ile Tyr Gly Ala Leu Lys Lys Ile Met  
                   100                  105                  110

Arg Thr Glu Ala Ser Gly Gly Pro Cys Glu Ala Ser Thr Ser  
                   115                  120                  125

&lt;210&gt; 1077

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1077

Arg Met Glu Leu Arg Thr Gly Ser Val Gly Ser Gln Ala Val Ala Arg  
   1                  5                  10                  15

Arg Met Asp Gly Asp Ser Arg Asp Gly Gly Gly Gly Lys Asp Ala Thr  
                   20                  25                  30

Gly Ser

&lt;210&gt; 1078

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1078

542

Pro Val Asp Ser Val Lys Thr Arg Met Gln Ser Leu Ser Pro Asp Pro  
 1 5 10 15

Lys Ala Gln Tyr Thr Ser Ile Tyr Gly Ala Leu  
 20 25

&lt;210&gt; 1079

&lt;211&gt; 424

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (152)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (314)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (359)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1079

Met Lys Leu Leu Gly Glu Cys Ser Ser Ser Ile Asp Ser Val Lys Arg  
 1 5 10 15

Leu Glu His Lys Leu Lys Glu Glu Glu Glu Ser Leu Pro Gly Phe Val  
 20 25 30

Asn Leu His Ser Thr Glu Thr Gln Thr Ala Gly Val Ile Asp Arg Trp  
 35 40 45

Glu Leu Leu Gln Ala Gln Ala Leu Ser Lys Glu Leu Arg Met Lys Gln  
 50 55 60

Asn Leu Gln Lys Trp Gln Gln Phe Asn Ser Asp Leu Asn Ser Ile Trp  
 65 70 75 80

Ala Trp Leu Gly Asp Thr Glu Glu Glu Leu Glu Gln Leu Gln Arg Leu  
 85 90 95

Glu Leu Ser Thr Asp Ile Gln Thr Ile Glu Leu Gln Ile Lys Lys Leu  
 100 105 110

Lys Glu Leu Gln Lys Ala Val Asp His Arg Lys Ala Ile Ile Leu Ser  
 115 120 125

Ile Asn Leu Cys Ser Pro Glu Phe Thr Gln Ala Asp Ser Lys Glu Ser  
 130 135 140

Arg Asp Leu Gln Asp Arg Leu Xaa Gln Met Asn Gly Arg Trp Asp Arg  
 145 150 155 160

543

Val Cys Ser Leu Leu Glu Glu Trp Arg Gly Leu Leu Gln Asp Ala Leu  
 165 170 175  
 Met Gln Cys Gln Gly Phe His Glu Met Ser His Gly Leu Leu Leu Met  
 180 185 190  
 Leu Glu Asn Ile Asp Arg Arg Lys Asn Glu Ile Val Pro Ile Asp Ser  
 195 200 205  
 Asn Leu Asp Ala Glu Ile Leu Gln Asp His His Lys Gln Leu Met Gln  
 210 215 220  
 Ile Lys His Glu Leu Leu Glu Ser Gln Leu Arg Val Ala Ser Leu Gln  
 225 230 235 240  
 Asp Met Ser Cys Gln Leu Leu Val Asn Ala Glu Gly Thr Asp Cys Leu  
 245 250 255  
 Glu Ala Lys Glu Lys Val His Val Ile Gly Asn Arg Leu Lys Leu Leu  
 260 265 270  
 Leu Lys Glu Val Ser Arg His Ile Lys Glu Leu Glu Lys Leu Leu Asp  
 275 280 285  
 Val Ser Ser Ser Gln Gln Asp Leu Ser Ser Trp Ser Ser Ala Asp Glu  
 290 295 300  
 Leu Asp Thr Ser Gly Ser Val Ser Pro Xaa Ser Gly Arg Ser Thr Pro  
 305 310 315 320  
 Asn Arg Gln Lys Thr Pro Arg Gly Lys Cys Ser Leu Ser Gln Pro Gly  
 325 330 335  
 Pro Ser Val Ser Ser Pro His Ser Arg Ser Thr Lys Gly Gly Ser Asp  
 340 345 350  
 Ser Ser Leu Ser Glu Pro Xaa Pro Gly Arg Ser Gly Arg Gly Phe Leu  
 355 360 365  
 Phe Arg Val Leu Arg Ala Ala Leu Pro Leu Gln Leu Leu Leu Leu Leu  
 370 375 380  
 Leu Ile Gly Leu Ala Cys Leu Val Pro Met Ser Glu Glu Asp Tyr Ser  
 385 390 395 400  
 Cys Ala Leu Ser Asn Asn Phe Ala Arg Ser Phe His Pro Met Leu Arg  
 405 410 415  
 Tyr Thr Asn Gly Pro Pro Pro Leu  
 420

&lt;210&gt; 1080

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1080

544

Met Lys Leu Leu Gly Glu Cys Ser Ser Ser Ile Asp Ser Val Lys Arg  
 1 5 10 15  
 Leu Glu His Lys Leu Lys Glu Glu Glu Glu Ser Leu Pro Gly Phe Val  
 20 25 30  
 Asn Leu His Ser Thr Glu Thr Gln Thr Ala Gly Val Ile Asp Arg Trp  
 35 40 45  
 Glu Leu Leu Gln Ala Gln Ala Leu Ser Lys Glu Leu Arg Met Lys Gln  
 50 55 60  
 Asn Leu Gln Lys Trp Gln Gln Phe Asn Ser Asp Leu Asn Ser Ile Trp  
 65 70 75 80  
 Ala Trp Leu Gly Asp Thr Glu Glu Glu Leu Glu Gln Leu Gln Arg Leu  
 85 90 95  
 Glu Leu Ser Thr Asp Ile Gln Thr Ile Glu Leu Gln Ile Lys  
 100 105 110

&lt;210&gt; 1081

&lt;211&gt; 136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1081

Lys Leu Lys Glu Leu Gln Lys Ala Val Asp His Arg Lys Ala Ile Ile  
 1 5 10 15  
 Leu Ser Ile Asn Leu Cys Ser Pro Glu Phe Thr Gln Ala Asp Ser Lys  
 20 25 30  
 Glu Ser Arg Asp Leu Gln Asp Arg Leu Xaa Gln Met Asn Gly Arg Trp  
 35 40 45  
 Asp Arg Val Cys Ser Leu Leu Glu Glu Trp Arg Gly Leu Leu Gln Asp  
 50 55 60  
 Ala Leu Met Gln Cys Gln Gly Phe His Glu Met Ser His Gly Leu Leu  
 65 70 75 80  
 Leu Met Leu Glu Asn Ile Asp Arg Arg Lys Asn Glu Ile Val Pro Ile  
 85 90 95  
 Asp Ser Asn Leu Asp Ala Glu Ile Leu Gln Asp His His Lys Gln Leu  
 100 105 110  
 Met Gln Ile Lys His Glu Leu Leu Glu Ser Gln Leu Arg Val Ala Ser  
 115 120 125  
 Leu Gln Asp Met Ser Cys Gln Leu

545

130

135

&lt;210&gt; 1082

&lt;211&gt; 105

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1082

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Asp | Met | Ser | Cys | Gln | Leu | Leu | Val | Asn | Ala | Glu | Gly | Thr | Asp | Cys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Glu | Ala | Lys | Glu | Lys | Val | His | Val | Ile | Gly | Asn | Arg | Leu | Lys | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Lys | Glu | Val | Ser | Arg | His | Ile | Lys | Glu | Leu | Glu | Lys | Leu | Leu |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Val | Ser | Ser | Ser | Gln | Gln | Asp | Leu | Ser | Ser | Trp | Ser | Ser | Ala | Asp |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Asp | Thr | Ser | Gly | Ser | Val | Ser | Pro | Xaa | Ser | Gly | Arg | Ser | Thr |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Asn | Arg | Gln | Lys | Thr | Pro | Arg | Gly | Lys | Cys | Ser | Leu | Ser | Gln | Pro |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Ser | Val | Ser | Ser | Pro | His | Ser |
|     |     |     | 100 |     |     |     |     | 105 |

&lt;210&gt; 1083

&lt;211&gt; 73

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1083

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ser | Ser | Leu | Ser | Glu | Pro | Xaa | Pro | Gly | Arg | Ser | Gly | Arg | Gly | Phe |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Arg | Val | Leu | Arg | Ala | Ala | Leu | Pro | Leu | Gln | Leu | Leu | Leu | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Ile | Gly | Leu | Ala | Cys | Leu | Val | Pro | Met | Ser | Glu | Glu | Asp | Tyr |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Cys | Ala | Leu | Ser | Asn | Asn | Phe | Ala | Arg | Ser | Phe | His | Pro | Met | Leu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

546

Arg Tyr Thr Asn Gly Pro Pro Pro Leu

65 70

&lt;210&gt; 1084

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1084

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Arg | Phe | Leu | Pro | Pro | Gly | Ser | Cys | Xaa | Leu | Ile | Arg | Gly | Pro | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Pro | Arg | Val | Thr | Asp | Pro | Thr | Thr | Gly | Gln | Ser | Leu | Asp | Asp | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Phe | Gln | Ile | Gln | Gln | Thr | Glu | Asn | Ile | Ile | Arg | Ser | Lys | Thr | Pro |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Pro | Glu | Leu | Asp | Thr | Ser | Tyr | Lys | Gly | Tyr |
| 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |

&lt;210&gt; 1085

&lt;211&gt; 215

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1085

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ile | Ser | Ala | Ser | Arg | Leu | Glu | Ser | Ile | Gly | Thr | Ile | Ser | Phe | Phe |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Ser | Met | Phe | Ser | Ser | Ile | Arg | Ser | Lys | Pro | Trp | Leu | Ile | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Lys | Pro | Trp | His | Cys | Ile | Arg | Ala | Ser | Cys | Ser | Arg | Pro | Arg | His |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Ser | Arg | Glu | His | Thr | Arg | Ser | Gln | Arg | Pro | Phe | Ile | Cys | Xaa |
| 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Arg | Ser | Cys | Arg | Ser | Arg | Leu | Ser | Leu | Leu | Ser | Ala | Trp | Val | Asn |
| 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Leu | Gln | Arg | Leu | Met | Glu | Arg | Met | Met | Ala | Leu | Arg | Trp | Ser |
|     |     |     |     |     | 85  |     |     |     | 90  |     |     |     |     | 95  |     |



547

Thr Ala Phe Trp Ser Ser Leu Ser Phe Leu Ile Trp Ser Ser Met Val  
 100 105 110  
 Trp Met Ser Val Leu Ser Ser Arg Arg Trp Ser Cys Ser Asn Ser Ser  
 115 120 125  
 Ser Val Ser Pro Ser Gln Ala Gln Met Leu Phe Lys Ser Glu Leu Asn  
 130 135 140  
 Cys Cys His Phe Trp Arg Phe Cys Phe Ile Leu Asn Ser Leu Leu Asn  
 145 150 155 160  
 Ala Trp Ala Trp Arg Ser Ser His Arg Ser Ile Thr Pro Ala Val Trp  
 165 170 175  
 Val Ser Val Leu Cys Arg Leu Thr Lys Pro Gly Arg Leu Ser Ser Ser  
 180 185 190  
 Ser Phe Ser Leu Cys Ser Ser Leu Phe Thr Glu Ser Ile Leu Leu Leu  
 195 200 205  
 His Ser Pro Ser Ser Phe Met  
 210 215

<210> 1086  
 <211> 35  
 <212> PRT  
 <213> Homo sapiens

<400> 1086  
 Thr Ala Phe Trp Ser Ser Leu Ser Phe Leu Ile Trp Ser Ser Met Val  
 1 5 10 15  
 Trp Met Ser Val Leu Ser Ser Arg Arg Trp Ser Cys Ser Asn Ser Ser  
 20 25 30  
 Ser Val Ser  
 35

<210> 1087  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 1087  
 Leu Leu Asn Ala Trp Ala Trp Arg Ser Ser His Arg Ser Ile Thr Pro  
 1 5 10 15  
 Ala Val Trp Val Ser Val Leu Cys Arg Leu  
 20 25

<210> 1088  
 <211> 171  
 <212> PRT  
 <213> Homo sapiens

548

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (94)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1088

Leu Ala Arg His Val Leu Gln Arg Gly Tyr Ser Glu Leu Gly Phe Gln  
 1 5 10 15

Gln Leu Met Leu Tyr Leu His Lys Leu Phe Val Met Val Leu Lys Tyr  
 20 25 30

Leu Cys Ile Lys Val Arg Ile Asn Arg Asp Asn Phe Ile Phe Pro Ser  
 35 40 45

Val Asn Val Leu Gln His Lys Lys Gln Thr Met Ala His Phe Met Glu  
 50 55 60

Thr Leu Ala Leu His Gln Gly Ile Leu Gln Gln Ala Pro Pro Leu Leu  
 65 70 75 80

Gln Gln Arg Ala His Ser Val Pro Ala Pro Ile His Leu Xaa Gln Ala  
 85 90 95

Ile Leu Gln Val Pro Ala Leu Leu Ala Val Ser Leu Gly Glu Leu Arg  
 100 105 110

Ala Ala Glu Ile Asp Gly Glu Asp Asp Gly Phe Ala Val Val His Ser  
 115 120 125

Phe Leu Glu Leu Leu Glu Leu Phe Asp Leu Glu Leu Asp Gly Leu Asp  
 130 135 140

Val Ser Ala Glu Phe Gln Thr Leu Glu Leu Phe Gln Leu Leu Leu Arg  
 145 150 155 160

Val Pro Gln Pro Gly Pro Asp Ala Val Gln Val  
 165 170

&lt;210&gt; 1089

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1089

Tyr Ser Glu Leu Gly Phe Gln Gln Leu Met Leu Tyr Leu His Lys Leu  
 1 5 10 15

Phe Val Met Val Leu Lys Tyr Leu Cys Ile Lys Val  
 20 25

&lt;210&gt; 1090

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

549

&lt;400&gt; 1090

Val His Ser Phe Leu Glu Leu Leu Glu Leu Phe Asp Leu Glu Leu Asp  
 1 5 10 15

Gly Leu Asp Val Ser Ala Glu Phe Gln Thr Leu Glu Leu  
 20 25

&lt;210&gt; 1091

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1091

Ala Met Val Cys Phe Leu Cys Trp Arg Thr Leu Thr Glu Gly Lys  
 1 5 10 15

&lt;210&gt; 1092

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1092

Gly Ala Gly Val Gly Thr Ala Met Pro Arg Val Pro Gln Ser Ala Gly  
 1 5 10 15

Gly Ala Val Thr Trp Trp Gly Val Gly Leu Ser Gln Pro Ser Ser Val  
 20 25 30

Gln Gly Gly Ala Arg Pro Gly Thr Val Pro Gly Thr Pro Gly Pro Leu  
 35 40 45

Pro Gly Leu Ser Pro Ala Pro Pro Pro Gln His Pro Pro Pro Leu Pro  
 50 55 60

Lys Leu Phe Leu Leu Cys Leu Ser Xaa Ser Leu Pro Gln Asp Phe Ser  
 65 70 75 80

Leu Leu Leu Cys Leu Ser Leu Asp Pro Cys Pro Ser Ser Thr Ser Asp  
 85 90 95

Leu

&lt;210&gt; 1093

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1093

550

Gly Thr Val Pro Gly Thr Pro Gly Pro Leu Pro Gly Leu Ser Pro Ala  
 1 5 10 15

Pro Pro Pro Gln His Pro Pro Pro Leu Pro Lys Leu Phe Leu  
 20 25 30

&lt;210&gt; 1094

&lt;211&gt; 158

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (83)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (136)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1094

Ala Pro Ser Arg Cys Arg Arg Ser Val Val Gln Val Pro Tyr Ser Ala  
 1 5 10 15

Phe Ser Ser Cys Ser Trp Thr Pro Thr Ala Leu Arg Arg Gly Val Leu  
 20 25 30

Leu Tyr Ala Gly Leu Ser Thr Ser Ser Ala Ser Lys Ala Gln Gly Trp  
 35 40 45

His Cys Leu Gly Leu Glu Tyr Pro Ser Gly Ala Ile Met Glu Val Arg  
 50 55 60

Gly Arg Gly Gly Asp Arg Tyr Ala Gln Gly Pro Ser Lys Cys Trp Arg  
 65 70 75 80

Gly Cys Xaa Leu Val Gly Ser Gly Ser Val Thr Ala Ile Leu Cys Pro  
 85 90 95

Gly Trp Gly Lys Ala Trp Asp Ser Ala Arg His Pro Arg Thr Pro Ser  
 100 105 110

Arg Leu Val Ser Cys Ser Thr Ala Ser Thr Pro Pro Thr Pro Ala Gln  
 115 120 125

Ala Val Ser Pro Leu Pro Leu Xaa Phe Pro Ala Pro Gly Leu Leu Ser  
 130 135 140

Ser Pro Leu Pro Leu Leu Gly Pro Leu Pro Phe Leu Tyr Leu  
 145 150 155

&lt;210&gt; 1095

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

551

&lt;400&gt; 1095

Thr Ala Leu Arg Arg Gly Val Leu Leu Tyr Ala Gly Leu Ser Thr Ser  
 1 5 10 15

Ser Ala Ser Lys Ala Gln Gly Trp His Cys Leu Gly Leu Glu Tyr Pro  
 20 25 30

Ser Gly Ala Ile Met  
 35

&lt;210&gt; 1096

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1096

Ala Ile Leu Cys Pro Gly Trp Gly Lys Ala Trp Asp Ser Ala Arg His  
 1 5 10 15

Pro Arg Thr Pro Ser Arg Leu Val Ser Cys Ser Thr Ala Ser Thr Pro  
 20 25 30

Pro

&lt;210&gt; 1097

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (28)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (67)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1097

Pro Pro Val Phe Met Ala Ser His Arg Pro Xaa Gly Met Glu Pro Gly  
 1 5 10 15

Glu Trp Arg Phe Val Leu Val His Ile Ala Phe Xaa Cys Ala Trp Asp  
 20 25 30

Leu Val Cys Glu His Val Ser Val Cys Ser Gln Val Arg Gly Arg Gly  
 35 40 45

552

Arg Ala Gly Val Gln Gly Glu Ala Glu Glu Lys Arg Glu Val Leu Gly  
 50 55 60

Gln Gly Xaa Arg Glu Ala Glu Glu Lys Gln Leu Gly Gln Gly Trp Gly  
 65 70 75 80

Val Leu Arg Arg Trp Ser Arg Arg Gln Ala Trp Lys Gly Ser Trp Gly  
 85 90 95

Ala Trp His Cys Pro Arg Pro Cys Pro Thr Leu Asp Arg Gly Trp Leu  
 100 105 110

<210> 1098  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 1098  
 His Val Ser Val Cys Ser Gln Val Arg Gly Arg Gly Arg Ala Gly Val  
 1 5 10 15

Gln Gly Glu Ala Glu Glu Lys Arg Glu Val Leu Gly Gln  
 20 25

<210> 1099  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 1099  
 Met Lys Leu Leu Ile Cys Gly Asn Tyr Leu Ala Pro Ser His Ser Glu  
 1 5 10 15

Ser Ser Arg Arg Cys Cys Leu Leu Cys Phe Tyr Pro Leu Cys Leu Glu  
 20 25 30

Ile Asn Phe Gly Met Lys Val Phe Leu Ser Met Pro Phe Leu Val Leu  
 35 40 45

Phe Gln Ser Leu Ile Gln Glu Asp  
 50 55

<210> 1100  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 1100  
 Phe Ser Ser Pro Gln Gly Leu Lys Phe Arg Ser Lys Ser Ser Leu Ala  
 1 5 10 15

Asn Tyr Leu His Lys Asn Gly Glu Thr Ser Leu Lys Pro Glu Asp Phe

553

20                      25                      30  
 Asp Phe Thr Val Leu Ser Lys Arg Gly Ile Lys Ser Arg Tyr Lys Asp  
       35                      40                      45  
 Cys Ser  
       50

<210> 1101  
 <211> 137  
 <212> PRT  
 <213> Homo sapiens

<400> 1101  
 Glu Leu Leu Cys Tyr Ile Cys Trp Lys Asn Thr Gly Leu Phe Ser Phe  
       1                      5                      10                      15  
 Phe Leu Ser Val Phe Arg Gly Met Val Ser Ser Val Lys Ser Phe Leu  
           20                      25                      30  
 Val Gly Glu Gln Leu Leu Ser Ile Ser Glu Pro Arg Phe Lys Met Ser  
           35                      40                      45  
 Val Cys Lys Cys Ser Phe Leu Ser Thr Thr Ser Thr Phe Val Pro Ile  
           50                      55                      60  
 Ser Ser Asp Ser Lys Lys Val Ser Ser Tyr Phe Ser Leu Cys Ser Glu  
       65                      70                      75                      80  
 Ser Leu Ala Glu Gln Asn Leu Phe Met Met Pro Glu Val Phe Cys Ser  
           85                      90                      95  
 Glu Gln Lys Phe Asp Pro Glu Leu Asn Asp Leu Ser Phe Phe Phe Thr  
           100                      105                      110  
 Arg Leu Phe Ser Ser Leu Val Thr Leu Arg Val Ser Pro His Ala Pro  
           115                      120                      125  
 Ala Ser Glu Met Gln Thr Val Leu Ser  
           130                      135

<210> 1102  
 <211> 36  
 <212> PRT  
 <213> Homo sapiens

<400> 1102  
 Thr Phe Val Pro Ile Ser Ser Asp Ser Lys Lys Val Ser Ser Tyr Phe  
       1                      5                      10                      15  
 Ser Leu Cys Ser Glu Ser Leu Ala Glu Gln Asn Leu Phe Met Met Pro  
           20                      25                      30  
 Glu Val Phe Cys  
           35

.554

&lt;210&gt; 1103

&lt;211&gt; 271

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (112)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (231)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1103

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Leu | Leu | Val | Lys | Tyr | Ser | Ala | Asn | Glu | Glu | Asn | Lys | Tyr | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Leu | Pro | Thr | Thr | Val | Asn | Val | Cys | Ser | Glu | Leu | Val | Lys | Leu | Val |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Cys | Val | Leu | Val | Ser | Phe | Cys | Val | Ile | Lys | Lys | Asp | His | Gln | Ser |
|     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Asn | Leu | Lys | Tyr | Ala | Ser | Trp | Lys | Glu | Phe | Ser | Asp | Phe | Met | Lys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Ser | Ile | Pro | Ala | Phe | Leu | Tyr | Phe | Leu | Asp | Asn | Leu | Ile | Val | Phe |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Val | Leu | Ser | Tyr | Leu | Gln | Pro | Ala | Met | Ala | Val | Ile | Phe | Ser | Asn |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ser | Ile | Ile | Thr | Thr | Ala | Leu | Leu | Phe | Arg | Ile | Val | Leu | Lys | Xaa |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Leu | Asn | Trp | Ile | Gln | Trp | Ala | Ser | Leu | Leu | Thr | Leu | Phe | Leu | Ser |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Val | Ala | Leu | Thr | Ala | Gly | Thr | Lys | Thr | Leu | Gln | His | Asn | Leu | Ala |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Arg | Gly | Phe | His | His | Asp | Ala | Phe | Phe | Ser | Pro | Ser | Asn | Ser | Cys |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Phe | Arg | Asn | Glu | Cys | Pro | Arg | Lys | Asp | Asn | Cys | Thr | Ala | Lys |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Trp | Thr | Phe | Pro | Glu | Ala | Lys | Trp | Asn | Thr | Thr | Ala | Arg | Val | Phe |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | His | Ile | Arg | Leu | Gly | Met | Gly | His | Val | Leu | Ile | Ile | Val | Gln | Cys |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ile | Ser | Ser | Met | Ala | Asn | Ile | Tyr | Asn | Glu | Lys | Ile | Leu | Lys | Glu |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |



555

Gly Asn Gln Leu Thr Glu Xaa Ile Phe Ile Gln Asn Ser Lys Leu Tyr  
 225 230 235 240

Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg Ser  
 245 250 255

Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe Tyr Gly His Ser  
 260 265 270

&lt;210&gt; 1104

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1104

Thr Val Asn Val Cys Ser Glu Leu Val Lys Leu Val Phe Cys Val Leu  
 1 5 10 15

Val Ser Phe Cys Val Ile Lys Lys Asp His Gln Ser Arg Asn  
 20 25 30

&lt;210&gt; 1105

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1105

Leu Ile Val Phe Tyr Val Leu Ser Tyr Leu Gln Pro Ala Met Ala Val  
 1 5 10 15

Ile Phe Ser Asn Phe Ser Ile Ile Thr Thr Ala Leu Leu Phe Arg  
 20 25 30

&lt;210&gt; 1106

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1106

Phe Phe Ser Pro Ser Asn Ser Cys Leu Leu Phe Arg Asn Glu Cys Pro  
 1 5 10 15

Arg Lys Asp Asn Cys Thr Ala Lys Glu Trp Thr  
 20 25

&lt;210&gt; 1107

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1107

Tyr Phe Phe Gly Ile Leu Phe Asn Gly Leu Thr Leu Gly Leu Gln Arg  
 1 5 10 15

556

Ser Asn Arg Asp Gln Ile Lys Asn Cys Gly Phe Phe  
 20 25

&lt;210&gt; 1108

&lt;211&gt; 94

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1108

Asn Ser Val Pro Asn Leu Gln Thr Leu Ala Val Leu Thr Glu Ala Ile  
 1 5 10 15

Gly Pro Glu Pro Ala Ile Pro Arg Xaa Pro Arg Glu Pro Pro Val Ala  
 20 25 30

Thr Ser Thr Pro Ala Thr Pro Ser Ala Gly Pro Gln Pro Leu Pro Thr  
 35 40 45

Gly Thr Val Leu Val Pro Gly Gly Pro Ala Pro Pro Cys Leu Gly Glu  
 50 55 60

Ala Trp Ala Leu Leu Leu Pro Pro Cys Arg Pro Ser Leu Thr Ser Cys  
 65 70 75 80

Phe Trp Ser Pro Arg Pro Ser Pro Trp Lys Glu Thr Gly Val  
 85 90

&lt;210&gt; 1109

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1109

Val Thr Ala Gly Arg Val Gly Gly Gly Gly Pro Met Pro Pro Gln Gly  
 1 5 10 15

Lys Val Gly Gln Asp Pro Gln Gly Pro Ala Arg Ser Arg Leu Gly Gly  
 20 25 30

Ala Gly Ala Arg Gln Arg Val Trp Gln Val Trp Thr Trp Gln Gln Ala  
 35 40 45

Ala Pro Gly Gly Xaa Gly Gly Trp Arg Ala Leu Gly Gln Trp Pro Gln  
 50 55 60

557

<210> 1110  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 1110  
Ser Thr Pro Ala Thr Pro Ser Ala Gly Pro Gln Pro Leu Pro Thr Gly  
1 5 10 15  
Thr Val Leu Val Pro Gly Gly Pro Ala Pro  
20 25

<210> 1111  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 1111  
Gln Asp Pro Gln Gly Pro Ala Arg Ser Arg Leu Gly Gly Ala Gly Ala  
1 5 10 15  
Arg Gln Arg

<210> 1112  
<211> 40  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (28)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1112  
Ala Leu Gln Leu Ala Phe Tyr Pro Asp Ala Val Glu Glu Trp Leu Glu  
1 5 10 15  
Glu Asn Val His Pro Ser Leu Gln Arg Leu Gln Xaa Leu Leu Gln Asp  
20 25 30  
Leu Ser Glu Val Ser Ala Pro Pro  
35 40

<210> 1113  
<211> 30  
<212> PRT  
<213> Homo sapiens

<400> 1113  
Cys His Pro Pro Ala Leu Ala Gly Thr Leu Leu Arg Thr Pro Glu Gly

558

1                      5                      10                      15  
 Arg Ala His Ala Arg Gly Leu Leu Leu Glu Ala Gly Gly Ala  
                     20                      25                      30

<210> 1114  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 1114  
 Gly Ser Ser Ser Thr Arg Ser Trp Phe Ser Thr Ser Ser Pro Gln Arg  
   1                      5                      10                      15  
 Ser Ala Ser Trp His Ser Gly Ala Pro Ser Cys Arg Ser Trp Arg Leu  
                     20                      25                      30  
 Pro Cys Ser Trp Leu Ser Thr Arg Met Pro Trp Arg Ser Gly Trp Arg  
                     35                      40                      45  
 Lys Thr Cys Thr Pro Ala Cys Ser Gly Cys Lys  
                     50                      55

<210> 1115  
 <211> 83  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (24)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1115  
 Ala Ser Thr Leu Gln Pro Ser Leu Ser Pro Ser Ser Pro Pro Leu Xaa  
   1                      5                      10                      15  
 Pro Pro Val Glu Thr Ala Val Xaa Ser Arg Ala Leu Arg Arg Glu Gly  
                     20                      25                      30  
 Ala Gly Ser Phe Pro Gly Ser Asn Ile Leu Ala Leu Val Thr Gln Val  
                     35                      40                      45  
 Ser Leu His Leu Arg Ser Ser Val Asp Ala Leu Leu Glu Gly Asn Arg  
                     50                      55                      60  
 Tyr Val Thr Gly Trp Phe Ser Pro Tyr His Arg Gln Arg Lys Leu Ile  
                     65                      70                      75                      80  
 His Pro Val

<210> 1116  
<211> 292  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (11)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (15)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (35)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (36)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (39)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (40)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (45)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (91)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (255)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (256)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

560

&lt;221&gt; SITE

&lt;222&gt; (257)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (258)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1116

Pro Leu Gly Pro Glu Lys Ala Gly Leu Ala Xaa Pro Leu Val Xaa His  
 1 5 10 15  
 Ala Ala Arg Pro Cys Pro Ser Thr Ser Leu Gln Ser Gln Cys Ser Pro  
 20 25 30  
 Ser Leu Xaa Xaa Glu Pro Xaa Xaa Pro Pro Arg Ser Xaa Val Ile Ser  
 35 40 45  
 Gly Gly Phe Asp Glu Asp Val Lys Ala Lys Val Glu Asn Leu Leu Gly  
 50 55 60  
 Ile Ser Ser Leu Glu Lys Thr Asp Pro Val Arg Gln Ala Pro Cys Ser  
 65 70 75 80  
 Pro Pro Cys Pro Leu Leu Pro Leu Pro Phe Xaa Arg Pro Trp Arg Gln  
 85 90 95  
 Leu Phe Ser Ala Gly Leu Ser Ala Gly Arg Gly Pro Ala Pro Ser Leu  
 100 105 110  
 Ala Ala Thr Ser Leu Pro Leu Ser His Lys Ser Ala Ser Ile Cys Ala  
 115 120 125  
 Ala Leu Trp Met Arg Cys Trp Arg Ala Thr Gly Met Ser Leu Ala Gly  
 130 135 140  
 Ser Ala Pro Thr Thr Ala Ser Gly Ser Ser Ser Thr Arg Ser Trp Phe  
 145 150 155 160  
 Ser Thr Ser Ser Pro Gln Arg Ser Ala Ser Trp His Ser Gly Ala Pro  
 165 170 175  
 Ser Cys Arg Ser Trp Arg Leu Pro Cys Ser Trp Leu Ser Thr Arg Met  
 180 185 190  
 Pro Trp Arg Ser Gly Trp Arg Lys Thr Cys Thr Pro Ala Cys Ser Gly  
 195 200 205  
 Cys Lys Leu Cys Cys Arg Thr Ser Ala Arg Cys Leu Pro Pro Arg Cys  
 210 215 220  
 His Pro Pro Ala Leu Ala Gly Thr Leu Leu Arg Thr Pro Glu Gly Arg  
 225 230 235 240  
 Ala His Ala Arg Gly Leu Leu Leu Glu Ala Gly Gly Ala Leu Xaa Xaa  
 245 250 255

561

Xaa Xaa Ala Trp Ala Ile Arg Pro Thr Trp Ala Ser Cys Pro Leu Ala  
                   260                  265                  270

Gln Gln Cys Leu Ala His Thr Gln Phe Leu Arg Ala Leu Gly Ser Pro  
                   275                  280                  285

Trp Gly Arg Asp  
           290

<210> 1117

<211> 235

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (52)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (164)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (209)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (210)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (211)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 1117

Phe Gln Glu Asp Leu Met Lys Met Leu Lys Arg Lys Trp Arg Thr Phe  
   1                  5                  10                  15

Ser Gly Phe Pro Ala Trp Lys Lys Arg Thr Leu Leu Gly Lys His Pro  
                   20                  25                  30

Ala Ala Leu Pro Val Pro Phe Phe Pro Ser Pro Ser Pro Ala Arg Gly  
                   35                  40                  45

Asp Ser Cys Xaa Gln Gln Gly Ser Pro Gln Gly Gly Gly Arg Leu Leu  
           50                  55                  60

Pro Trp Gln Gln His Pro Cys Pro Cys His Thr Ser Gln Pro Pro Ser  
   65                  70                  75                  80

Ala Gln Leu Cys Gly Cys Ala Ala Gly Gly Gln Gln Val Cys His Trp  
                   85                  90                  95

562

Leu Val Gln Pro Leu Pro Pro Pro Ala Glu Ala His Pro Pro Gly His  
 100 105 110

Gly Ser Ala His Pro Ala Arg Ser Ala Gln Pro Pro Gly Thr Val Glu  
 115 120 125

His Pro Arg Ala Gly Ala Gly Gly Cys Pro Ala Ala Gly Phe Leu Pro  
 130 135 140

Gly Cys Arg Gly Gly Val Ala Gly Gly Lys Arg Ala Pro Gln Pro Ala  
 145 150 155 160

Ala Ala Ala Xaa Ser Ala Ala Gly Pro Gln Arg Gly Val Cys Pro Pro  
 165 170 175

Ala Ala Thr His Gln Pro Trp Gln Gly Arg Cys Ser Gly Pro Leu Arg  
 180 185 190

Gly Glu Leu Met Pro Gly Gly Ser Cys Trp Arg Leu Gly Gly Leu Cys  
 195 200 205

Xaa Xaa Xaa Trp Pro Gly Gln Tyr Gly Pro Arg Gly Arg Arg Ala Leu  
 210 215 220

Trp Pro Ser Ser Val Leu Pro Thr Leu Ser Ser  
 225 230 235

<210> 1118

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (151)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (197)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (198)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (202)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (203)

<223> Xaa equals any of the naturally occurring L-amino acids



563

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (206)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (207)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (227)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1118

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Leu | Pro | Ser | Gly | Val | Leu | Ser | Asn | Val | Pro | Ala | Arg | Ala | Gly | Gly |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Gln | Arg | Gly | Gly | Arg | His | Leu | Ala | Glu | Val | Leu | Gln | Gln | Ser | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Pro | Leu | Gln | Ala | Gly | Val | His | Val | Phe | Leu | Gln | Pro | Leu | Leu | His |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ile | Arg | Val | Glu | Ser | Gln | Leu | Gln | Gly | Ser | Leu | Gln | Leu | Leu | His |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gly | Ala | Pro | Leu | Cys | Gln | Glu | Ala | Glu | Arg | Cys | Gly | Leu | Asp | Val |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asn | His | Asp | Arg | Val | Asp | Glu | Leu | Pro | Leu | Ala | Val | Val | Gly | Ala |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Pro | Ala | Ser | Asp | Ile | Pro | Val | Ala | Leu | Gln | Gln | Arg | Ile | His | Arg |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ala | Gln | Met | Glu | Ala | Asp | Leu | Cys | Asp | Lys | Gly | Lys | Asp | Val | Ala |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Arg | Glu | Gly | Ala | Gly | Pro | Leu | Pro | Ala | Glu | Ser | Pro | Ala | Glu | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Cys | Leu | His | Gly | Arg | Xaa | Lys | Gly | Arg | Gly | Arg | Arg | Gly | Gln | Gly |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Leu | Gln | Gly | Ala | Cys | Leu | Thr | Gly | Ser | Val | Phe | Ser | Arg | Leu | Glu |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Pro | Arg | Arg | Phe | Ser | Thr | Phe | Ala | Leu | Thr | Ser | Ser | Ser | Asn | Pro |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Ile | Thr | Xaa | Xaa | Arg | Gly | Gly | Xaa | Xaa | Gly | Ser | Xaa | Xaa | Arg |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gly | Leu | His | Trp | Asp | Cys | Arg | Leu | Val | Leu | Gly | His | Gly | Arg | Ala |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |

564

Ala Trp Xaa Thr Asn Gly Gln Ala Asn Pro Ala Phe Ser Gly Pro Lys  
 225 230 235 240

Gly

<210> 1119  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 1119  
 Arg Gln Leu Phe Ser Ala Gly Leu Ser Ala Gly Arg Gly Pro Ala Pro  
 1 5 10 15

Ser Leu Ala Ala Thr Ser Leu Pro Leu Ser His Lys Ser  
 20 25

<210> 1120  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 1120  
 Glu Leu Pro Leu Ala Val Val Gly Ala Glu Pro Ala Ser Asp Ile Pro  
 1 5 10 15

Val Ala Leu Gln Gln Arg Ile His Arg Ala Ala Gln  
 20 25

<210> 1121  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 1121  
 Gln Pro Pro Gly Thr Val Glu His Pro Arg Ala Gly Ala Gly Gly Cys  
 1 5 10 15

Pro Ala Ala Gly Phe Leu Pro Gly Cys Arg Gly  
 20 25

<210> 1122  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 1122  
 Ser Val Phe Glu Arg Thr Asn Glu Phe Arg Asp Val Leu Trp Ser Ser  
 1 5 10 15

Ile

565

&lt;210&gt; 1123

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1123

Gly Val Val Gln Val Thr Phe Met Ser Ser Val Ser Arg Val Thr Trp  
 1 5 10 15

Gly Cys Gln Pro Ser Ile Cys Pro Gly Ala Pro Pro Ala Ala Ala Leu  
 20 25 30

Ala Gly Gly Leu Arg Leu Leu Phe Glu Arg Glu Leu Phe Gly Leu Pro  
 35 40 45

Val Ser Ser Pro Leu Ile Cys Ser Phe Leu Glu His His Pro Arg Thr  
 50 55 60

Ser Pro Pro Pro Ser Asp Cys Glu Leu Leu Glu Gly Arg Ser Cys Val  
 65 70 75 80

Leu Leu Phe Ile Phe Leu Ser Pro Glu Pro Cys Thr Asp Pro Gly Met  
 85 90 95

Trp

&lt;210&gt; 1124

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1124

Ser Lys Gln Ile His Ser Phe Val His Ser Phe Ile His Leu Phe Asn  
 1 5 10 15

Thr His Leu Leu Ser Thr Tyr His Ile Pro Gly Ser Val Gln Gly Ser  
 20 25 30

Gly Asp Arg Lys Met Asn Arg Arg Thr Gln Leu Leu Pro Ser Arg Ser  
 35 40 45

Ser Gln Ser Asp Gly Gly Gly Asp Val Leu Gly Trp Cys Ser Lys Lys  
 50 55 60

Glu Gln Ile Arg Gly Glu Glu Thr Gly Arg Pro Asn Ser Ser Leu Ser  
 65 70 75 80

Lys Arg Ser Leu Arg Pro Pro Ala Arg Ala Ala Ala Gly Gly Ala Pro  
 85 90 95

Gly Gln Met Leu Gly  
 100

566

<210> 1125  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 1125  
 Val Thr Trp Gly Cys Gln Pro Ser Ile Cys Pro Gly Ala Pro Pro Ala  
     1                    5                    10                    15  
 Ala Ala Leu Ala Gly Gly Leu Arg Leu Leu Phe Glu  
                     20                    25

<210> 1126  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 1126  
 Glu Gln Ile Arg Gly Glu Glu Thr Gly Arg Pro Asn Ser Ser Leu Ser  
     1                    5                    10                    15  
 Lys Arg Ser Leu Arg Pro Pro  
                     20

<210> 1127  
 <211> 130  
 <212> PRT  
 <213> Homo sapiens

<400> 1127  
 Gln Trp Glu His Leu Leu Leu Leu Pro His Leu Leu Arg Gly Ala His  
     1                    5                    10                    15  
 Arg Asp Pro Gly Asp Ile Leu Pro Leu Ala Pro Arg Ser Glu Cys Arg  
                     20                    25                    30  
 Ala Asn Ser Ile Lys Glu Tyr Gln Lys Ser Ile Trp Lys Val Tyr Val  
                     35                    40                    45  
 Val Arg Leu Arg Leu Leu Lys Pro Gln Pro Asn Ile Ile Pro Thr Val  
     50                    55                    60  
 Lys Lys Ile Val Leu Leu Ala Gly Trp Ala Leu Phe Leu Phe Leu Ala  
     65                    70                    75                    80  
 Tyr Lys Val Ser Lys Thr Asp Arg Glu Tyr Gln Glu Tyr Asn Pro Tyr  
                     85                    90                    95  
 Glu Val Leu Asn Leu Asp Pro Gly Ala Thr Val Ala Glu Ile Lys Lys  
                     100                    105                    110  
 Gln Tyr Arg Leu Leu Ser Leu Lys Tyr His Pro Asp Lys Gly Gly Asp  
     115                    120                    125  
 Glu Val  
     130

567

&lt;210&gt; 1128

&lt;211&gt; 65

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1128

Glu Glu Arg Gly Gly Gly Gly Ala Met Ala Gly Gln Gln Phe Gln  
 1 5 10 15

Tyr Asp Asp Ser Gly Asn Thr Phe Phe Tyr Phe Leu Thr Ser Phe Val  
 20 25 30

Gly Leu Ile Val Ile Pro Ala Thr Tyr Tyr Leu Trp Pro Arg Asp Gln  
 35 40 45

Asn Ala Glu Gln Ile Arg Leu Lys Asn Ile Arg Lys Val Tyr Gly Arg  
 50 55 60

Cys  
 65

&lt;210&gt; 1129

&lt;211&gt; 220

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1129

Arg Leu Tyr Thr Gly Cys Val Ile Phe Asp Leu Val Ser Asn Arg Ala  
 1 5 10 15

Leu Ser Phe Arg Cys Met Leu Cys Cys Asn Ser Cys His Ser Ala Ser  
 20 25 30

Ser Ser Leu Phe Cys Phe Ser Ser Cys Ser Leu Ser Glu Ser Leu Ser  
 35 40 45

Leu Pro Ser Ser Phe Ser Leu Trp Glu Ser Leu Leu Val Ser Ser Ser  
 50 55 60

Ser Glu Ser Leu Pro Leu Ser Glu Thr Ser Ser Ser Ser Ser Phe Thr  
 65 70 75 80

Ala Ala Ser Phe Pro Thr Thr Pro Phe Ala Cys Phe Cys Phe Cys Cys  
 85 90 95

Phe Asp Cys Gly Asn Ser Thr Gly Val Gly Phe Phe Phe Lys Gly Phe  
 100 105 110

Phe Phe Phe Asp Leu Ala Val Phe Leu Gly Pro Leu Leu Phe Cys Cys  
 115 120 125

His Pro Pro Phe Val Leu Phe Leu Leu Val Ser Pro Cys Pro Ser Ser  
 130 135 140

Ala Gly Cys Ser Ser Ala Ala Gln Met Asp Cys Ser Phe Ser Asn Thr

568

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Ser | Ala | Ile | Val | Cys | Leu | Val | Asn | Leu | Thr | Asn | Thr | Val | Thr | Lys | Asp |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Pro | Thr | Val | Met | Leu | Leu | Leu | Ser | Ser | Ser | Ser | Asn | Thr | Cys | Asp | Phe |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Ile | Ser | Met | Val | Thr | Tyr | Gly | Lys | Leu | Pro | Arg | Thr | Ala | Ile | Thr | Ser |
|     |     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ser | Tyr | Phe | Ser | Ser | Ser | Arg | Lys | Cys | Ser | Arg | Val |     |     |     |     |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |

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<210> 1130
<211> 35
<212> PRT
<213> Homo sapiens
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<400> 1130  
Tyr Gln Lys Ser Ile Trp Lys Val Tyr Val Val Arg Leu Arg Leu Leu  
1 5 10 15

Lys Pro Gln Pro Asn Ile Ile Pro Thr Val Lys Lys Ile Val Leu Leu  
20 25 30

Ala Gly Trp  
35

```
<210> 1131
<211> 35
<212> PRT
<213> Homo sapiens
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<400> 1131  
Cys His Pro Pro Phe Val Leu Phe Leu Leu Val Ser Pro Cys Pro Ser  
1 5 10 15

Ser Ala Gly Cys Ser Ser Ala Ala Gln Met Asp Cys Ser Phe Ser Asn  
20 25 30

Thr Ser Ala  
35

```
<210> 1132
<211> 26
<212> PRT
<213> Homo sapiens
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<400> 1132  
Gly Thr Ser Leu Asp Ala Ala Ala Thr Ala Ala Ser Leu Ser Pro Arg  
1 5 10 15

Gly Cys Arg Leu Arg Thr Pro Ser Ser Asp  
20 25

569

&lt;210&gt; 1133

&lt;211&gt; 99

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1133

Gln Ile Gln Arg His Thr Arg Ala Pro Lys Gln Leu Ile Pro Leu Met  
 1 5 10 15

Thr Pro Arg Arg Ser Leu Arg Asp His Pro Gln Ala Gln Thr Ser Arg  
 20 25 30

Gln Thr Pro Arg Pro Ser Ser His Leu Val Phe Met Arg Met Thr Pro  
 35 40 45

Ser Ser Met Met Asn Thr Pro Ser Gly Asn Gly Gly Cys Trp Ser Gln  
 50 55 60

Leu Cys Cys Ser Ser Gln Ala Ser Ser Ser Ser Pro Val Ala Ser Ala  
 65 70 75 80

Gly Ser Cys Pro Gly Tyr Ala Gly Ile Ile Ala Gly Glu Ser Ile Arg  
 85 90 95

Asn Arg Ser

&lt;210&gt; 1134

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1134

Pro Arg Arg Ser Leu Arg Asp His Pro Gln Ala Gln Thr Ser Arg Gln  
 1 5 10 15

Thr Pro Arg Pro Ser Ser His Leu Val Phe Met  
 20 25

&lt;210&gt; 1135

&lt;211&gt; 129

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1135

Thr His Pro Pro Glu Thr Gly Ala Val Gly Arg Ser Cys Ala Val His  
 1 5 10 15

His Arg His His His Pro His Gln Trp Gln Val Gln Ala Ala Val Pro

570

20                      25                      30  
 Val Met Pro Glu Ser Leu Gln Val Ser Pro Ser Glu Thr Gly Ala Asp  
                     35                      40                      45  
 Asn Xaa Leu Gly Thr Arg Arg Pro Ser Pro Leu Pro Ala His Arg Ala  
                     50                      55                      60  
 Gln Pro Pro Ala Ser Pro Arg Arg Ala Trp Pro Glu Arg Glu Asp Thr  
                     65                      70                      75                      80  
 Asp Asp Glu Ala Gly Ala Arg Ala Ala Gly Pro Ser Leu Leu Pro Pro  
                     85                      90                      95  
 Pro Thr Leu Pro Ala Pro Glu Gly Tyr Leu Ala Pro Trp Gly Leu Ser  
                     100                      105                      110  
 Leu Lys Leu Ser Pro Leu Leu Arg Gln Lys Val Lys His Cys Gly Leu  
                     115                      120                      125

Cys

&lt;210&gt; 1136

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1136

Pro Glu Ser Leu Gln Val Ser Pro Ser Glu Thr Gly Ala Asp Asn Xaa  
                     1                      5                      10                      15

Leu Gly Thr Arg Pro Ser Pro Leu Pro Ala His Arg Ala Gln Pro  
                     20                      25                      30

Pro Ala Ser Pro  
                     35

&lt;210&gt; 1137

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1137

Gly Thr Ala Pro Lys Ala Pro Gly Ser Leu Gln Gly Arg Ala Gly Leu  
                     1                      5                      10                      15

Gly Glu Val Gly Asp Ser Asp Arg Gln Pro Trp Leu Gln Leu His His  
                     20                      25                      30

Leu Cys Leu Pro Ser Leu Ala Arg Leu Phe Glu Gly Met Gln Glu Ala



571

35                      40                      45  
 Gly His Gly Glu Leu Ala Gly Gly Leu Val Phe Gly Cys Pro Ala Gly  
     50                      55                      60  
 Cys Gln Leu Leu Phe Leu Met Asp Ser Pro Ala Met Ile Pro Ala  
     65                      70                      75

<210> 1138  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 1138  
 Gly Glu Val Gly Asp Ser Asp Arg Gln Pro Trp Leu Gln Leu His His  
     1                      5                      10                      15  
 Leu Cys Leu Pro Ser Leu Ala Arg Leu Phe Glu Gly Met Gln Glu Ala  
     20                      25                      30

Gly His

<210> 1139  
 <211> 86  
 <212> PRT  
 <213> Homo sapiens

<400> 1139  
 Gly Ser Gly Gly Leu Ser Gly Arg Leu Cys Leu Gly Met Val Ser Gln  
     1                      5                      10                      15  
 Arg Ala Ser Trp Cys His Gln Trp Asp Glu Leu Leu Trp Cys Ser Cys  
     20                      25                      30  
 Val Ser Leu Asp Leu Ser Leu Glu Ala His Pro Phe Leu Pro Val Ala  
     35                      40                      45  
 Gly Ser Gly Ser Gly Val Val Val Phe His Gln Gln Ala Arg Leu Gly  
     50                      55                      60  
 Leu Glu Arg Trp Ala Gly Val Leu Cys Arg Leu His Leu Gly Leu Val  
     65                      70                      75                      80  
 Ser Gly Pro Glu Cys Pro  
     85

<210> 1140  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 1140  
 Gln Trp Asp Glu Leu Leu Trp Cys Ser Cys Val Ser Leu Asp Leu Ser  
     1                      5                      10                      15

.572

Leu Glu Ala His Pro Phe Leu Pro Val Ala Gly Ser Gly Ser Gly Val  
 20 25 30

Val Val Phe His Gln Gln Ala Arg Leu  
 35 40

&lt;210&gt; 1141

&lt;211&gt; 247

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1141

Met Arg Pro Asp Trp Lys Ala Gly Ala Gly Pro Gly Gly Pro Pro Gln  
 1 5 10 15

Lys Pro Ala Pro Ser Ser Gln Arg Lys Pro Pro Ala Arg Pro Ser Ala  
 20 25 30

Ala Ala Ala Ala Ile Ala Val Ala Ala Ala Glu Glu Glu Arg Arg Leu  
 35 40 45

Arg Gln Arg Asn Arg Leu Arg Leu Glu Glu Asp Lys Pro Ala Val Glu  
 50 55 60

Arg Cys Leu Glu Glu Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp  
 65 70 75 80

Ala Leu Leu Arg Arg Leu Arg Gly Pro Arg Val Gln Glu His Glu Asp  
 85 90 95

Ser Gly Asp Ser Glu Val Glu Asn Glu Ala Lys Gly Asn Phe Pro Pro  
 100 105 110

Gln Lys Lys Pro Val Trp Val Asp Glu Glu Asp Glu Asp Glu Glu Met  
 115 120 125

Val Asp Met Met Asn Asn Arg Phe Arg Lys Asp Met Met Lys Asn Ala  
 130 135 140

Ser Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg Leu Lys Glu  
 145 150 155 160

Glu Phe Gln His Ala Met Gly Gly Val Pro Ala Trp Ala Glu Thr Thr  
 165 170 175

Lys Arg Lys Thr Ser Ser Asp Asp Glu Ser Glu Glu Asp Glu Asp Asp  
 180 185 190

Leu Leu Gln Arg Thr Gly Asn Phe Ile Ser Thr Ser Thr Ser Leu Pro  
 195 200 205

Arg Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn Ala Glu Arg  
 210 215 220

Pro Thr Val Ala Arg Ile Ser Ile Cys Ala Val Pro Ser Arg Cys Thr  
 225 230 235 240

573

Asp Cys Asp Gly Cys Trp Asp  
245

&lt;210&gt; 1142

&lt;211&gt; 180

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1142

Cys Leu Glu Glu Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp Ala  
1 5 10 15

Leu Leu Arg Arg Leu Arg Gly Pro Arg Val Gln Glu His Glu Asp Ser  
20 25 30

Gly Asp Ser Glu Val Glu Asn Glu Ala Lys Gly Asn Phe Pro Pro Gln  
35 40 45

Lys Lys Pro Val Trp Val Asp Glu Glu Asp Glu Asp Glu Glu Met Val  
50 55 60

Asp Met Met Asn Asn Arg Phe Arg Lys Asp Met Met Lys Asn Ala Ser  
65 70 75 80

Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg Leu Lys Glu Glu  
85 90 95

Phe Gln His Ala Met Gly Gly Val Pro Ala Trp Ala Glu Thr Thr Lys  
100 105 110

Arg Lys Thr Ser Ser Asp Asp Glu Ser Glu Glu Asp Glu Asp Asp Leu  
115 120 125

Leu Gln Arg Thr Gly Asn Phe Ile Ser Thr Ser Thr Ser Leu Pro Arg  
130 135 140

Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn Ala Glu Arg Pro  
145 150 155 160

Thr Val Ala Arg Ile Ser Ile Cys Ala Val Pro Ser Arg Cys Thr Asp  
165 170 175

Cys Asp Gly Cys  
180

&lt;210&gt; 1143

&lt;211&gt; 218

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1143

Leu Lys Glu Lys Ile Val Arg Ser Phe Glu Val Ser Pro Asp Gly Ser  
1 5 10 15

Phe Leu Leu Ile Asn Gly Ile Ala Gly Tyr Leu His Leu Leu Ala Met

574

|         |                         |                         |                 |     |    |  |
|---------|-------------------------|-------------------------|-----------------|-----|----|--|
|         | 20                      |                         | 25              |     | 30 |  |
| Lys Thr | Lys Glu Leu Ile Gly     | Ser Met Lys Ile Asn Gly | Arg Val Ala     |     |    |  |
|         | 35                      | 40                      | 45              |     |    |  |
| Ala Ser | Thr Phe Ser Ser Asp     | Ser Lys Lys Val Tyr     | Ala Ser Ser Gly |     |    |  |
|         | 50                      | 55                      | 60              |     |    |  |
| Asp Gly | Glu Val Tyr Val Trp     | Asp Val Asn Ser Arg     | Lys Cys Leu Asn |     |    |  |
|         | 65                      | 70                      | 75              | 80  |    |  |
| Arg Phe | Val Asp Glu Gly Ser     | Leu Tyr Gly Leu Ser     | Ile Ala Thr Ser |     |    |  |
|         | 85                      | 90                      | 95              |     |    |  |
| Arg Asn | Gly Gln Tyr Val Ala Cys | Gly Ser Asn Cys Gly     | Val Val Asn     |     |    |  |
|         | 100                     | 105                     | 110             |     |    |  |
| Ile Tyr | Asn Gln Asp Ser Cys     | Leu Gln Glu Thr Asn     | Pro Lys Pro Ile |     |    |  |
|         | 115                     | 120                     | 125             |     |    |  |
| Lys Ala | Ile Met Asn Leu Val Thr | Gly Val Thr Ser Leu     | Thr Phe Asn     |     |    |  |
|         | 130                     | 135                     | 140             |     |    |  |
| Pro Thr | Thr Glu Ile Leu Ala Ile | Ala Ser Glu Lys Met     | Lys Glu Ala     |     |    |  |
|         | 145                     | 150                     | 155             | 160 |    |  |
| Val Arg | Leu Val His Leu Pro Ser | Cys Thr Val Phe Ser     | Asn Phe Pro     |     |    |  |
|         | 165                     | 170                     | 175             |     |    |  |
| Val Ile | Lys Asn Lys Asn Ile Ser | His Val His Thr Met     | Asp Phe Ser     |     |    |  |
|         | 180                     | 185                     | 190             |     |    |  |
| Pro Arg | Ser Gly Tyr Phe Ala Leu | Gly Asn Glu Lys Gly     | Lys Ala Leu     |     |    |  |
|         | 195                     | 200                     | 205             |     |    |  |
| Met Tyr | Arg Leu His His Tyr     | Ser Asp Phe             |                 |     |    |  |
|         | 210                     | 215                     |                 |     |    |  |

&lt;210&gt; 1144

&lt;211&gt; 167

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1144

|         |                     |                     |                 |
|---------|---------------------|---------------------|-----------------|
| Lys Ile | Asn Gly Arg Val Ala | Ala Ser Thr Phe Ser | Ser Asp Ser Lys |
| 1       | 5                   | 10                  | 15              |
| Lys Val | Tyr Ala Ser Ser Gly | Asp Gly Glu Val Tyr | Val Trp Asp Val |
|         | 20                  | 25                  | 30              |
| Asn Ser | Arg Lys Cys Leu Asn | Arg Phe Val Asp Glu | Gly Ser Leu Tyr |
|         | 35                  | 40                  | 45              |
| Gly Leu | Ser Ile Ala Thr Ser | Arg Asn Gly Gln Tyr | Val Ala Cys Gly |
|         | 50                  | 55                  | 60              |
| Ser Asn | Cys Gly Val Val Asn | Ile Tyr Asn Gln Asp | Ser Cys Leu Gln |

575

65                      70                      75                      80  
 Glu Thr Asn Pro Lys Pro Ile Lys Ala Ile Met Asn Leu Val Thr Gly  
                                  85                                   90                                   95  
 Val Thr Ser Leu Thr Phe Asn Pro Thr Thr Glu Ile Leu Ala Ile Ala  
                                  100                                   105                                   110  
 Ser Glu Lys Met Lys Glu Ala Val Arg Leu Val His Leu Pro Ser Cys  
                                  115                                   120                                   125  
 Thr Val Phe Ser Asn Phe Pro Val Ile Lys Asn Lys Asn Ile Ser His  
                                  130                                   135                                   140  
 Val His Thr Met Asp Phe Ser Pro Arg Ser Gly Tyr Phe Ala Leu Gly  
 145                                   150                                   155                                   160  
 Asn Glu Lys Gly Lys Ala Leu  
                                  165

<210> 1145  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<400> 1145  
 Trp Leu Leu Gly Leu Asp Asn Ala Val Ser Leu Phe Gln Val Asp Gly  
   1                                 5                                 10                                 15  
 Lys Thr Asn Pro Lys Ile Gln Ser Ile Tyr Leu Glu Arg Phe Pro Ile  
                                  20                                 25                                 30  
 Phe Lys Ala Cys Phe Ser Ala Asn Gly Glu Glu Val Leu Ala Thr Ser  
                                  35                                 40                                 45  
 Thr His Ser Lys Val Leu Tyr Val Tyr Asp  
   50                                 55

<210> 1146  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 1146  
 Leu Val Phe Gly Asp Val Glu Asn Asp Glu Asp Ala Leu Leu Arg Arg  
   1                                 5                                 10                                 15  
 Leu Arg Gly Pro Arg Val Gln  
                                  20

<210> 1147  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

576

&lt;400&gt; 1147

Lys Asn Ala Ser Glu Ser Lys Leu Ser Lys Asp Asn Leu Lys Lys Arg  
 1 5 10 15

Leu Lys Glu Glu Phe Gln His Ala Met Gly Gly Val Pro  
 20 25

&lt;210&gt; 1148

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1148

Ser Leu Pro Arg Gly Ile Leu Lys Met Lys Asn Cys Gln His Ala Asn  
 1 5 10 15

Ala Glu Arg Pro Thr Val Ala  
 20

&lt;210&gt; 1149

&lt;211&gt; 246

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1149

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val  
 1 5 10 15

Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Leu His Ser  
 20 25 30

Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly  
 35 40 45

Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu  
 50 55 60

Lys Pro Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu  
 65 70 75 80

Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro  
 85 90 95

Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met  
 100 105 110

Leu Val Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro  
 115 120 125

Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Ser Phe  
 130 135 140

Pro Ala Gly Ala Ala Arg Pro Asp Pro Ser Tyr Ala Cys Leu Thr Pro  
 145 150 155 160

Cys Asp Ala Pro Thr Ser Pro Ser Leu Ser Thr Arg Ser Val Arg Thr

1.65

175

<210> 1150

<211> 228

<212> PRT

<213> Homo sapiens

<400> 1150

Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Leu His Ser Gln Pro  
1 5 10 15

Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly Ala Thr  
20 25 30

Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu Lys Pro  
35 40 45

Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu Glu Gly  
50 55 60

Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro Gly Phe  
65 70 75 80

Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met Leu Val  
85 90 95

Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro Leu Thr  
100 105 110

Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Ser Phe Pro Ala  
115 120 125

Gly Ala Ala Arg Pro Asp Pro Ser Tyr Ala Cys Leu Thr Pro Cys Asp  
130 135 140

Ala Pro Thr Ser Pro Ser Leu Ser Thr Arg Ser Val Arg Thr Pro Thr  
145 150 155 160

Pro Ala Thr Ser Gln Thr Pro Trp Cys Val Pro Ala Cys Arg Lys Gly  
165 170 175

Ala Arg Thr Pro Ala Arg Val Thr Pro Gly Ala Leu Trp Ser Val Thr

578

180 185 190

Ser Leu Phe Lys Ala Leu Ser Pro Gly Ala Arg Ile Arg Val Arg Ser  
 195 200 205

Pro Glu Ser Leu Val Ser Thr Arg Lys Ser Ala Asn Met Trp Thr Gly  
 210 215 220

Ser Arg Arg Arg  
 225

<210> 1151  
 <211> 74  
 <212> PRT  
 <213> Homo sapiens

<400> 1151  
 Cys Lys Leu His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr  
 1 5 10 15

Arg Leu Leu Cys Gly Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr  
 20 25 30

Ala Ala His Cys Leu Lys Pro Arg Tyr Ile Val His Leu Gly Gln His  
 35 40 45

Asn Leu Gln Lys Glu Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu  
 50 55 60

Ser Phe Pro His Pro Gly Phe Asn Asn Ser  
 65 70

<210> 1152  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (21)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (22)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1152  
 Val Leu Gln Gly Arg Tyr Phe Ser Pro Ile Leu Glu Met Arg Arg Leu  
 1 5 10 15

Arg Pro Glu Gly Xaa Xaa Asn Leu Pro Gly Gly Ser Arg Ala Gln Lys  
 20 25 30

Glu Pro Arg Gln Asp Leu Thr Leu Val Leu Trp Pro His Cys Pro His  
 35 40 45



579

Phe Ala Met Thr Arg Ser Tyr Val Pro Thr Lys Gln Cys Met Val Gln  
 50 55 60

Gly Ser Phe Tyr Cys Ile Phe Ile Phe Lys Gly Pro Val Gln Asn Trp  
 65 70 75 80

Cys

<210> 1153  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 1153  
 Cys Pro Arg Arg Thr Cys Val Arg Val Glu Lys Ser Arg Pro Phe  
 1 5 10 15

Gln Cys Gln Leu His Ser Ile Ser  
 20

<210> 1154  
 <211> 8  
 <212> PRT  
 <213> Homo sapiens

<400> 1154  
 Pro Lys Glu Pro Gly Val Pro Glu  
 1 5

<210> 1155  
 <211> 104  
 <212> PRT  
 <213> Homo sapiens

<400> 1155  
 Leu Gln Leu Lys Pro Arg Asp Pro Phe Ser Thr Leu Gly Pro Asn Ala  
 1 5 10 15

Val Leu Ser Pro Gln Arg Leu Val Leu Glu Thr Leu Ser Lys Leu Ser  
 20 25 30

Ile Gln Asp Asn Asn Val Asp Leu Ile Leu Ala Thr Pro Pro Phe Ser  
 35 40 45

Arg Leu Glu Lys Leu Tyr Ser Thr Met Val Arg Phe Leu Ser Asp Arg  
 50 55 60

Lys Asn Pro Val Cys Arg Arg Trp Leu Trp Tyr Cys Trp Pro Thr Trp  
 65 70 75 80

Leu Arg Gly Thr Ala Trp Gln Leu Val Pro Leu Gln Cys Arg Arg Ala  
 85 90 95

580

Val Ser Ala Thr Ser Trp Ala Ser  
100

<210> 1156  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 1156  
Arg Asp Pro Phe Ser Thr Leu Gly Pro Asn Ala Val Leu Ser Pro Gln  
1 5 10 15  
Arg Leu Val Leu Glu Thr Leu Ser Lys Leu Ser  
20 25

<210> 1157  
<211> 105  
<212> PRT  
<213> Homo sapiens

<400> 1157  
Glu Val Ile Ser Gly Leu Phe Ile Gln Ser Arg Arg Arg Glu Arg Gly  
1 5 10 15  
Gln Gly Val Val Gly Ser His Met Ile Leu Trp Gly Lys Ser Leu Phe  
20 25 30  
Phe Phe Ser Pro Gln Arg Leu Thr Lys Asn Ile Phe Lys Asn Tyr Ser  
35 40 45  
Leu Leu Leu Thr Gln Arg Phe Leu Phe Pro Cys Glu Thr Leu Leu Leu  
50 55 60  
Gln Tyr Val Tyr Ser Ile Arg Cys Thr Val Gln Tyr Met Lys Gly Ser  
65 70 75 80  
Thr Leu Tyr Cys Thr Gly Leu Ser Ser Glu Gln Gly Leu Phe Thr Thr  
85 90 95  
Ala Asn Phe Leu Ala Pro Ala Arg Leu  
100 105

<210> 1158  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 1158  
Ile Arg Cys Thr Val Gln Tyr Met Lys Gly Ser Thr Leu Tyr Cys Thr  
1 5 10 15  
Gly Leu Ser Ser Glu Gln Gly  
20

581

&lt;210&gt; 1159

&lt;211&gt; 211

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (153)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1159

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Pro | Ile | Ile | Asp | Gln | Val | Asn | Pro | Glu | Leu | His | Asp | Phe | Met | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ala | Glu | Val | Gly | Thr | Ile | Phe | Ala | Leu | Ser | Trp | Leu | Ile | Thr | Trp |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Gly | His | Val | Leu | Ser | Asp | Phe | Arg | His | Val | Val | Arg | Leu | Tyr | Asp |
|     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Phe | Leu | Ala | Cys | His | Pro | Leu | Met | Pro | Ile | Tyr | Phe | Ala | Ala | Val |
|     | 50  |     |     |     | 55  |     |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Val | Leu | Tyr | Arg | Glu | Gln | Glu | Val | Leu | Asp | Cys | Asp | Cys | Asp | Met |
| 65  |     |     |     | 70  |     |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ser | Val | His | His | Leu | Leu | Ser | Gln | Ile | Pro | Gln | Asp | Leu | Pro | Tyr |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Thr | Leu | Ile | Ser | Arg | Xaa | Glu | Thr | Phe | Leu | Phe | Ser | Phe | Pro | His |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Asn | Leu | Leu | Gly | Arg | Pro | Leu | Pro | Asn | Ser | Lys | Leu | Arg | Gly | Arg |
|     | 115 |     |     |     |     | 120 |     |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Pro | Leu | Leu | Ser | Lys | Thr | Leu | Ser | Trp | His | Gln | Pro | Ser | Arg | Gly |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ile | Trp | Cys | Cys | Gly | Ser | Gly | Xaa | Arg | Gly | Leu | Leu | Arg | Pro | Glu |
| 145 |     |     |     | 150 |     |     |     | 155 |     |     |     |     |     | 160 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Arg | Thr | Lys | Asp | Val | Leu | Thr | Lys | Pro | Arg | Thr | Asn | Arg | Phe | Val |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Leu | Ala | Val | Met | Gly | Leu | Thr | Val | Ala | Leu | Gly | Ala | Ala | Ala | Leu |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Val | Val | Lys | Ser | Ala | Leu | Glu | Trp | Ala | Pro | Lys | Phe | Gln | Leu | Gln |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |
|-----|-----|-----|
| Leu | Phe | Pro |
|     | 210 |     |

582

&lt;210&gt; 1160

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1160

Cys Pro Glu Phe Phe Ile Pro Ala Thr Leu Pro Cys Pro Phe Val Phe  
 1 5 10 15  
 Ala Phe Thr Ser Glu Ala Ser Ser Arg Ala Tyr Leu Thr Gln Arg Gly  
 20 25 30  
 Pro Gly Gly Leu Ala Gln Asn Leu Met Pro Leu Pro Val Gly Phe Trp  
 35 40 45  
 Met Gly Ser Leu Pro Pro Pro Trp Cys Trp Arg Lys Trp Val Ser Glu  
 50 55 60  
 Ala Cys Ser Cys Phe Cys  
 65 70

&lt;210&gt; 1161

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1161

Cys Arg Gln Ala Gly Ala Val Arg Gly His Pro Met Phe Gln Phe Thr  
 1 5 10 15  
 Phe Tyr Gly Val Thr Xaa Arg Phe Pro Val Thr Arg Ala Ala Gln Ala  
 20 25 30  
 Gln Gln Val Ala Lys Ala Ala Ala Ser Phe Arg Asn Pro Leu Pro Pro  
 35 40 45  
 Thr Pro Gly Arg Trp Gln Arg Ala His Pro Lys Ala His Trp Glu Arg  
 50 55 60  
 His Lys Ile Leu Cys Gln Ala Pro Arg Ser Pro Leu Cys Gln Val Gly  
 65 70 75 80  
 Ser Ala Thr Gly Leu  
 85

&lt;210&gt; 1162

&lt;211&gt; 217

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

583

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (109)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (159)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1162

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ile | Leu | Asn | Tyr | Leu | Met | Pro | Ile | Ile | Asp | Gln | Val | Asn | Pro | Glu |
| 1   |     |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | His | Asp | Phe | Met | Gln | Ser | Ala | Glu | Val | Gly | Thr | Ile | Phe | Ala | Leu |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Trp | Leu | Ile | Thr | Trp | Phe | Gly | His | Val | Leu | Ser | Asp | Phe | Arg | His |
|     | 35  |     |     |     |     | 40  |     |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Arg | Leu | Tyr | Asp | Phe | Phe | Leu | Ala | Cys | His | Pro | Leu | Met | Pro |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Tyr | Phe | Ala | Ala | Val | Ile | Val | Leu | Tyr | Arg | Glu | Gln | Glu | Val | Leu |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Cys | Asp | Cys | Asp | Met | Ala | Ser | Val | His | His | Leu | Leu | Ser | Gln | Ile |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Gln | Asp | Leu | Pro | Tyr | Glu | Thr | Leu | Ile | Ser | Arg | Xaa | Glu | Thr | Phe |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Ser | Phe | Pro | His | Pro | Asn | Leu | Leu | Gly | Arg | Pro | Leu | Pro | Asn |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Lys | Leu | Arg | Gly | Arg | Gln | Pro | Leu | Leu | Ser | Lys | Thr | Leu | Ser | Trp |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Gln | Pro | Ser | Arg | Gly | Leu | Ile | Trp | Cys | Cys | Gly | Ser | Gly | Xaa | Arg |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Leu | Leu | Arg | Pro | Glu | Asp | Arg | Thr | Lys | Asp | Val | Leu | Thr | Lys | Pro |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Thr | Asn | Arg | Phe | Val | Lys | Leu | Ala | Val | Met | Gly | Leu | Thr | Val | Ala |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gly | Ala | Ala | Ala | Leu | Ala | Val | Val | Lys | Ser | Ala | Leu | Glu | Trp | Ala |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     |     | 205 |     |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Lys | Phe | Gln | Leu | Gln | Leu | Phe | Pro |
|     | 210 |     |     |     |     | 215 |     |     |

&lt;210&gt; 1163

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

584

&lt;400&gt; 1163

Ala Glu Val Gly Thr Ile Phe Ala Leu Ser Trp Leu Ile Thr Trp Phe  
1 5 10 15

Gly His Val Leu Ser Asp Phe Arg His Val Val Arg Leu Tyr Asp  
20 25 30

&lt;210&gt; 1164

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1164

Val Leu Thr Lys Pro Arg Thr Asn Arg Phe Val Lys Leu Ala Val Met  
1 5 10 15

Gly Leu Thr Val Ala Leu Gly Ala Ala Ala Leu Ala Val Val Lys Ser  
20 25 30

Ala

&lt;210&gt; 1165

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1165

Gly Phe Gly Ser Val Ser Ala Ala Gly Arg Arg Ser Gly Gly Thr Trp  
1 5 10 15

Gln Pro Val Gln  
20

&lt;210&gt; 1166

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1166

Pro Gly Gly Leu Ala Val Gly Ser Arg Trp Trp Ser Arg Ser Leu Thr  
1 5 10 15

&lt;210&gt; 1167

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1167

Leu Glu Pro Ser Arg Gln Arg Arg Pro Arg Arg Arg Gly Gly Thr Ser

585

1                      5                      10                      15  
 Arg Pro Glu Thr Asp Gln Arg Ala Lys Cys Trp Arg Gln Leu  
                     20                      25                      30

<210> 1168  
 <211> 11  
 <212> PRT  
 <213> Homo sapiens

<400> 1168  
 Val Cys Leu Arg Cys Gln Asn Arg Met Glu Asn  
       1                      5                      10

<210> 1169  
 <211> 367  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (22)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (102)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 1169  
 Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
       1                      5                      10                      15  
 Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
                     20                      25                      30  
 Ala Xaa Ala Gly Ala Phe Ser Pro Ala Ser Thr Thr Thr Thr Arg Arg  
                     35                      40                      45  
 His Leu Ser Ser Arg Asn Arg Pro Glu Gly Lys Val Leu Glu Thr Val  
                     50                      55                      60  
 Gly Val Phe Glu Val Pro Lys Gln Asn Gly Lys Tyr Glu Thr Gly Gln  
                     65                      70                      75                      80  
 Leu Phe Leu His Ser Ile Phe Gly Tyr Arg Gly Val Val Leu Phe Pro  
                     85                      90                      95  
 Trp Gln Ala Arg Leu Xaa Asp Arg Asp Val Ala Ser Ala Ala Pro Glu  
                     100                      105                      110

586

Lys Ala Glu Asn Pro Ala Gly His Gly Ser Lys Glu Val Lys Gly Lys  
           115                                  120                                  125  
 Thr His Thr Tyr Tyr Gln Val Leu Ile Asp Ala Arg Asp Cys Pro His  
           130                                  135                                  140  
 Ile Ser Gln Arg Ser Gln Thr Glu Ala Val Thr Phe Leu Ala Asn His  
   145                                  150                                  155                                  160  
 Asp Asp Ser Arg Ala Leu Tyr Ala Ile Pro Gly Leu Asp Tyr Val Ser  
                                   165                                  170                                  175  
 His Glu Asp Ile Leu Pro Tyr Thr Ser Thr Asp Gln Val Pro Ile Gln  
                                   180                                  185                                  190  
 His Glu Leu Phe Glu Arg Phe Leu Leu Tyr Asp Gln Thr Lys Ala Pro  
           195                                  200                                  205  
 Pro Phe Val Ala Arg Glu Thr Leu Arg Ala Trp Gln Glu Lys Asn His  
   210                                  215                                  220  
 Pro Trp Leu Glu Leu Ser Asp Val His Arg Glu Thr Thr Glu Asn Ile  
   225                                  230                                  235                                  240  
 Arg Val Thr Val Ile Pro Phe Tyr Met Gly Met Arg Glu Ala Gln Asn  
                                   245                                  250                                  255  
 Ser His Val Tyr Trp Trp Arg Tyr Cys Ile Arg Leu Glu Asn Leu Asp  
                                   260                                  265                                  270  
 Ser Asp Val Val Gln Leu Arg Glu Arg His Trp Arg Ile Phe Ser Leu  
           275                                  280                                  285  
 Ser Gly Thr Leu Glu Thr Val Arg Gly Arg Gly Val Val Gly Arg Glu  
   290                                  295                                  300  
 Pro Val Leu Ser Lys Glu Gln Pro Ala Phe Gln Tyr Ser Ser His Val  
   305                                  310                                  315                                  320  
 Ser Leu Gln Ala Ser Ser Gly His Met Trp Gly Thr Phe Arg Phe Glu  
                                   325                                  330                                  335  
 Arg Pro Asp Gly Ser His Phe Asp Val Arg Ile Pro Pro Phe Ser Leu  
           340                                  345                                  350  
 Glu Ser Asn Lys Asp Glu Lys Thr Pro Pro Ser Gly Leu His Trp  
   355                                  360                                  365

&lt;210&gt; 1170

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt; .

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids



587

&lt;400&gt; 1170

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
20 25 30

Ala

&lt;210&gt; 1171

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1171

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
20 25 30

Ala

&lt;210&gt; 1172

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1172

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
20 25 30

Ala

&lt;210&gt; 1173

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

588

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1173

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
20 25 30

Ala

&lt;210&gt; 1174

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1174

Met Ala Ala Cys Thr Ala Arg Arg Pro Gly Arg Gly Gln Pro Leu Val  
1 5 10 15

Val Pro Val Ala Asp Xaa Gly Pro Val Ala Lys Ala Ala Leu Cys Ala  
20 25 30

Ala

&lt;210&gt; 1175

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1175

Val Leu Glu Thr Val Gly Val Phe Glu Val Pro Lys Gln Asn Gly Lys  
1 5 10 15

Tyr Glu Thr Gly Gln Leu Phe Leu His Ser Ile Phe Gly Tyr Arg Gly  
20 25 30

Val Val Leu  
35

&lt;210&gt; 1176

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

589

&lt;400&gt; 1176

Gly Leu Asp Tyr Val Ser His Glu Asp Ile Leu Pro Tyr Thr Ser Thr  
1 5 10 15

&lt;210&gt; 1177

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1177

Asp Val His Arg Glu Thr Thr Glu Asn Ile Arg Val Thr Val Ile Pro  
1 5 10 15

Phe Tyr Met

&lt;210&gt; 1178

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1178

Trp Trp Arg Tyr Cys Ile Arg Leu Glu Asn Leu Asp Ser Asp Val Val  
1 5 10 15

Gln Leu Arg Glu Arg  
20

&lt;210&gt; 1179

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1179

Pro Ala Phe Gln Tyr Ser Ser His Val Ser Leu Gln Ala Ser Ser Gly  
1 5 10 15

His Met Trp Gly Thr Phe Arg Phe Glu Arg  
20 25

&lt;210&gt; 1180

&lt;211&gt; 230

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (114)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

590

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (182)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (194)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1180

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Leu | Pro | Ser | His | Lys | Arg | Arg | Cys | Phe | Cys | Leu | Val | Ile | Gln | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ser | Phe | Lys | Glu | Phe | Met | Leu | Asp | Gly | Asn | Leu | Ile | Ser | Gly | Gly |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gly | Glu | Asp | Val | Phe | Met | Ala | Asp | Ile | Val | Gln | Ala | Trp | Asp | Gly |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Glu | Gly | Pro | Thr | Val | Ile | Met | Val | Ser | Gln | Glu | Gly | His | Ser | Phe |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Leu | Arg | Ser | Leu | Arg | Tyr | Met | Trp | Ala | Val | Thr | Ser | Ile | Asn | Gln |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Leu | Ile | Val | Ser | Val | Ser | Phe | Ala | Phe | His | Leu | Leu | Gly | Ala | Met |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ser | Arg | Val | Leu | Cys | Phe | Phe | Trp | Ser | Cys | Arg | Ser | His | Ile | Pro |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Xaa | Gln | Ser | Gly | Leu | Pro | Gly | Lys | Gln | Asp | Asp | Thr | Ser | Val | Ala |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asn | Ala | Met | Lys | Glu | Lys | Leu | Pro | Gly | Leu | Ile | Phe | Ser | Ile | Leu |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Trp | His | Leu | Lys | His | Thr | Asn | Cys | Leu | Gln | His | Phe | Ala | Leu | Trp |
| 145 |     |     |     | 150 |     |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Val | Ser | Gly | Arg | Glu | Val | Pro | Pro | Arg | Arg | Arg | Gly | Arg | Arg | Trp |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Gly | Ser | Ser | Xaa | Gly | Arg | Ala | Gln | Ser | Gly | Leu | Gly | His | Arg |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Xaa | Val | Ser | Asp | Arg | Asp | His | Gln | Arg | Leu | Pro | Thr | Ala | Arg | Pro |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Gly | Cys | Thr | Gly | Cys | His | Val | Pro | Pro | Glu | Arg | Arg | Pro | Ala | Ala |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |

|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
| Asp | Thr | Glu | Pro | Asn | Pro |
| 225 |     |     |     | 230 |     |

&lt;210&gt; 1181

591

<211> 31  
<212> PRT  
<213> Homo sapiens

<400> 1181  
Lys Glu Phe Met Leu Asp Gly Asn Leu Ile Ser Gly Gly Val Gly Glu  
1 5 10 15  
Asp Val Phe Met Ala Asp Ile Val Gln Ala Trp Asp Gly Ile Glu  
20 25 30

<210> 1182  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 1182  
Ala Val Thr Ser Ile Asn Gln His Leu Ile Val Ser Val Ser Phe Ala  
1 5 10 15  
Phe His Leu Leu Gly Ala Met Ala Ser Arg Val Leu Cys  
20 25

<210> 1183  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 1183  
Thr Ala Arg Pro Pro Gly Cys Thr Gly Cys His Val Pro Pro Glu Arg  
1 5 10 15  
Arg Pro Ala Ala  
20

<210> 1184  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 1184  
Ser Leu Cys Cys Pro Glu Gly Ala Glu Gly Cys  
1 5 10

<210> 1185  
<211> 12  
<212> PRT  
<213> Homo sapiens

<400> 1185  
Gln Leu Lys Lys Thr His Tyr Asp Arg Pro Cys Pro  
1 5 10

592

<210> 1186  
 <211> 12  
 <212> PRT  
 <213> Homo sapiens

<400> 1186  
 Gln Leu Lys Lys Thr His Tyr Asp Arg Pro Cys Pro  
 1 5 10

<210> 1187  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 1187  
 Met Asn Arg Pro Cys Pro Phe Cys Leu Trp Lys Val Phe Pro Leu Leu  
 1 5 10 15

Leu Leu Leu His Glu Glu Leu Phe Pro Leu Pro Val Pro  
 20 25

<210> 1188  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 1188  
 Lys Glu Lys Thr Phe Thr Pro Arg Asn Ser Leu Cys Cys Pro Glu Gly  
 1 5 10 15

Ala Glu Gly Cys Ile Ala Gly Gly Asp Leu Gln Leu Lys Lys Thr His  
 20 25 30

Tyr

<210> 1189  
 <211> 170  
 <212> PRT  
 <213> Homo sapiens

<400> 1189  
 Ala Gln Arg Lys Lys Glu Met Val Leu Ser Glu Lys Val Ser Gln Leu  
 1 5 10 15

Met Glu Trp Thr Asn Lys Arg Pro Val Ile Arg Met Asn Gly Asp Lys  
 20 25 30

Phe Arg Arg Leu Val Lys Ala Pro Pro Arg Asn Tyr Ser Val Ile Val  
 35 40 45

Met Phe Thr Ala Leu Gln Leu His Arg Gln Cys Val Val Cys Lys Gln  
 50 55 60

Ala Asp Glu Glu Phe Gln Ile Leu Ala Asn Ser Trp Arg Tyr Ser Ser

593

|   |     |    |     |     |     |     |
|---|-----|----|-----|-----|-----|-----|
| 65  |     | 70 |     | 75  |     | 80  |
| Ala Phe Thr Asn Arg Ile Phe Phe Ala Met Val Asp Phe Asp Glu Gly |     |    |     |     |     |     |
|   | 85  |    |     | 90  |     | 95  |
| Ser Asp Val Phe Gln Met Leu Asn Met Asn Ser Ala Pro Thr Phe Ile |     |    |     |     |     |     |
|   | 100 |    | 105 |     | 110 |     |
| Asn Phe Pro Ala Lys Gly Lys Pro Lys Arg Gly Asp Thr Tyr Glu Leu |     |    |     |     |     |     |
|   | 115 |    | 120 |     | 125 |     |
| Gln Val Arg Gly Phe Ser Ala Glu Gln Ile Ala Arg Trp Ile Ala Asp |     |    |     |     |     |     |
|   | 130 |    | 135 |     | 140 |     |
| Arg Thr Asp Val Asn Ile Arg Val Ile Arg Pro Pro Asn Met Ala Ala |     |    |     |     |     |     |
|   | 145 |    | 150 |     | 155 | 160 |
| Arg Trp Arg Phe Trp Cys Val Ser Val Thr                         |     |    |     |     |     |     |
|   | 165 |    |     | 170 |     |     |

<210> 1190  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 1190  
 Met Val Val Ala Leu Leu Ile Val Cys Asp Val Pro Ser Ala Ser  
 1 5 10 15

<210> 1191  
 <211> 16  
 <212> PRT  
 <213> Homo sapiens

<400> 1191  
 Ala Gln Arg Lys Lys Glu Met Val Leu Ser Glu Lys Val Ser Gln Leu  
 1 5 10 15

<210> 1192  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 1192  
 Met Glu Trp Thr Asn Lys Arg Pro Val Ile Arg Met Asn Gly Asp Lys  
 1 5 10 15

Phe

<210> 1193

594

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1193

Arg Arg Leu Val Lys Ala Pro Pro Arg Asn Tyr Ser Val Ile Val Met  
 1 5 10 15

Phe Thr Ala Leu Gln Leu His Arg Gln Cys Val Val Cys Lys Gln Ala  
 20 25 30

Asp Glu Glu Phe Gln Ile Leu Ala Asn Ser Trp Arg Tyr Ser Ser Ala  
 35 40 45

Phe Thr Asn Arg Ile Phe Phe Ala  
 50 55

&lt;210&gt; 1194

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1194

Met Val Asp Phe Asp Glu Gly Ser Asp Val Phe Gln Met Leu Asn Met  
 1 5 10 15

Asn Ser Ala Pro Thr Phe Ile Asn Phe Pro Ala Lys Gly Lys Pro  
 20 25 30

&lt;210&gt; 1195

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1195

Lys Arg Gly Asp Thr Tyr Glu Leu Gln Val Arg Gly Phe Ser Ala Glu  
 1 5 10 15

Gln Ile Ala Arg Trp Ile Ala Asp Arg Thr Asp Val Asn Ile Arg Val  
 20 25 30

Ile Arg Pro Pro Asn  
 35

&lt;210&gt; 1196

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1196

Tyr Ala Gly Pro Leu Met Leu Gly Leu Leu Leu Ala Val Ile Gly Gly  
 1 5 10 15

Leu Val Tyr Leu Arg Arg Val Ile Trp Asn Phe Ser Leu Ile Lys Leu  
 20 25 30



595

Asp Gly Leu Leu Gln Leu Cys Val Leu Cys Leu Leu  
           35                          40

<210> 1197  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 1197  
 Asp Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp  
       1                  5                  10                  15

Ser

<210> 1198  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

<400> 1198  
 Cys Gln Glu Gly Ala Lys Asp Met Trp Asp Lys Leu Arg Lys Glu Ser  
       1                  5                  10                  15

Lys Asn Leu Asn  
                   20

<210> 1199  
 <211> 16  
 <212> PRT  
 <213> Homo sapiens

<400> 1199  
 Val Leu Leu Val Ser Leu Ser Ala Ala Leu Ala Thr Trp Leu Ser Phe  
       1                  5                  10                  15

<210> 1200  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<400> 1200  
 Met Gly Leu Lys Leu Asn Gly Arg Tyr Ile Ser Leu Ile Leu Ala Val  
       1                  5                  10                  15

Gln Ile Ala Tyr Leu Val Gln Ala Val Arg Ala Ala Gly Lys Cys Asp  
           20                  25                  30

Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp Ser  
           35                  40                  45

596

&lt;210&gt; 1201

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1201

Pro Ala Ala Trp Asp Asp Lys Thr Asn Ile Lys Thr Val Cys Thr Tyr  
 1 5 10 15

Trp Glu Asp Phe His Ser Cys Thr Val Thr Ala Leu Thr Asp Cys Gln  
 20 25 30

Glu Gly Ala Lys Asp Met Trp Asp Lys Leu Arg Lys Glu Ser Lys Asn  
 35 40 45

Leu Asn Ile Gln Gly Ser Leu Phe Glu Leu Cys Gly Ser Gly Asn Gly  
 50 55 60

Ala Ala Gly Ser Leu Leu Pro Ala Phe Pro Val Leu Leu Val Ser Leu  
 65 70 75 80

Ser Ala Ala Leu Ala Thr Trp Leu Ser Phe  
 85 90

&lt;210&gt; 1202

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (52)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

597

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1202

Met Gly Leu Lys Leu Asn Gly Arg Tyr Ile Ser Leu Ile Leu Ala Val  
 1 5 10 15

Gln Ile Ala Tyr Leu Val Gln Ala Val Arg Ala Ala Gly Lys Cys Asp  
 20 25 30

Ala Val Phe Lys Gly Phe Ser Asp Cys Leu Leu Lys Leu Gly Asp Ser  
 35 40 45

Xaa Xaa Xaa Xaa Xaa Pro Ala Ala Trp Asp Asp Lys Thr Asn Ile Lys  
 50 55 60

Thr Val Cys Thr Tyr Trp Glu Asp Phe His Ser Cys Thr Val Thr Ala  
 65 70 75 80

Leu Thr Asp Cys Gln Glu Gly Ala Lys Asp Met Trp Asp Lys Leu Arg  
 85 90 95

Lys Glu Ser Lys Asn Leu Asn Ile Gln Gly Ser Leu Phe Glu Leu Cys  
 100 105 110

Gly Ser Gly Asn Gly Ala Ala Gly Ser Leu Leu Pro Ala Phe Pro Val  
 115 120 125

Leu Leu Val Ser Leu Ser Ala Ala Leu Ala Thr Trp Leu Ser Phe  
 130 135 140

&lt;210&gt; 1203

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1203

Met Asn Ser Ala Ala Gly Phe Ser His Leu Asp Arg Arg Glu Arg Val  
 1 5 10 15

Leu Lys Leu Gly Glu Ser Phe Glu Lys Gln Pro Arg Cys Ala Ser Thr  
 20 25 30

Leu Cys

&lt;210&gt; 1204

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1204

Thr Ile Tyr Pro Thr Glu Glu Glu Leu Gln Ala Val Gln Lys Ile Val  
 1 5 10 15

Ser Ile Thr Glu Arg Ala Leu Lys Leu Val Ser Asp  
 20 25

598

&lt;210&gt; 1205

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1205

Arg Ala Leu Lys Gly Val Leu Arg Val Gly Val Leu Ala Lys Gly Leu  
1 5 10 15

Leu Leu Arg Gly Asp Arg Asn Val Asn Leu Val Leu Leu Cys  
20 25 30

&lt;210&gt; 1206

&lt;211&gt; 39

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1206

Ala Leu Ala Ala Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn  
1 5 10 15

Gly Leu Gln Ser Cys Val Ile Ile Ile Arg Ile Leu Arg Asp Leu Cys  
20 25 30

Gln Arg Val Pro Thr Trp Ser  
35

&lt;210&gt; 1207

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1207

Gly Asp Ala Leu Arg Arg Val Phe Glu Cys Ile Ser Ser Gly Ile Ile  
1 5 10 15

Leu

&lt;210&gt; 1208

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1208

Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro  
1 5 10 15

&lt;210&gt; 1209

599

&lt;211&gt; 342

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1209

Thr Ile Tyr Pro Thr Glu Glu Glu Leu Gln Ala Val Gln Lys Ile Val  
 1 5 10 15  
 Ser Ile Thr Glu Arg Ala Leu Lys Leu Val Ser Asp Ser Leu Ser Glu  
 20 25 30  
 His Glu Lys Asn Lys Asn Lys Glu Gly Asp Asp Lys Lys Glu Gly Gly  
 35 40 45  
 Lys Asp Arg Ala Leu Lys Gly Val Leu Arg Val Gly Val Leu Ala Lys  
 50 55 60  
 Gly Leu Leu Leu Arg Gly Asp Arg Asn Val Asn Leu Val Leu Leu Cys  
 65 70 75 80  
 Ser Glu Lys Pro Ser Lys Thr Leu Leu Ser Arg Ile Ala Glu Asn Leu  
 85 90 95  
 Pro Lys Gln Leu Ala Val Ile Ser Pro Glu Lys Tyr Asp Ile Lys Cys  
 100 105 110  
 Ala Val Ser Glu Ala Ala Ile Ile Leu Asn Ser Cys Val Glu Pro Lys  
 115 120 125  
 Met Gln Val Thr Ile Thr Leu Thr Ser Pro Ile Ile Arg Glu Glu Asn  
 130 135 140  
 Met Arg Glu Gly Asp Val Thr Ser Gly Met Val Lys Asp Pro Pro Asp  
 145 150 155 160  
 Val Leu Asp Arg Gln Lys Cys Leu Asp Ala Leu Ala Ala Leu Arg His  
 165 170 175  
 Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Gln Ser Cys Val Ile  
 180 185 190  
 Ile Ile Arg Ile Leu Arg Asp Leu Cys Gln Arg Val Pro Thr Trp Ser  
 195 200 205  
 Asp Phe Pro Ser Trp Ala Met Glu Leu Leu Val Glu Lys Ala Ile Ser  
 210 215 220  
 Ser Ala Ser Ser Pro Gln Ser Pro Gly Asp Ala Leu Arg Arg Val Phe  
 225 230 235 240  
 Glu Cys Ile Ser Ser Gly Ile Ile Leu Lys Gly Ser Pro Gly Leu Leu  
 245 250 255  
 Asp Pro Cys Glu Lys Asp Pro Phe Asp Thr Leu Ala Thr Met Thr Asp  
 260 265 270  
 Gln Gln Arg Glu Asp Ile Thr Ser Ser Ala Gln Phe Ala Leu Arg Leu  
 275 280 285

600

Leu Ala Phe Arg Gln Ile His Lys Val Leu Gly Met Asp Pro Leu Pro  
 290 295 300

Gln Met Ser Gln Arg Phe Asn Ile His Asn Asn Arg Lys Arg Arg Arg  
 305 310 315 320

Asp Ser Asp Gly Val Asp Gly Phe Glu Ala Glu Gly Lys Lys Asp Lys  
 325 330 335

Lys Asp Tyr Asp Asn Phe  
 340

<210> 1210

<211> 12

<212> PRT

<213> Homo sapiens

<400> 1210

Met Glu Arg His Pro Lys Lys Lys Met Cys Ser Asp  
 1 5 10

<210> 1211

<211> 31

<212> PRT

<213> Homo sapiens

<400> 1211

Gly Glu Asn Ser Ser Ser Asp Phe Phe Pro Leu Phe Leu Phe Tyr Phe  
 1 5 10 15

Leu Val Ala Leu Ala Ser Pro Pro Ile Phe Val Ser Phe Ile Asn  
 20 25 30

<210> 1212

<211> 24

<212> PRT

<213> Homo sapiens

<400> 1212

Met Gly Ser Gln His Ser Ala Ala Ala Arg Pro Ser Ser Cys Arg Arg  
 1 5 10 15

Lys Gln Glu Asp Asp Arg Asp Gly  
 20

<210> 1213

<211> 30

<212> PRT

<213> Homo sapiens

<400> 1213

Leu Leu Ala Glu Arg Glu Gln Glu Glu Ala Ile Ala Gln Phe Pro Tyr  
 1 5 10 15

601

Val Glu Phe Thr Gly Arg Asp Ser Ile Thr Cys Leu Thr Cys  
                   20                  25                  30

&lt;210&gt; 1214

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1214

Gln Gly Thr Gly Tyr Ile Pro Thr Glu Gln Val Asn Glu Leu Val Ala  
       1                  5                  10                  15

Leu Ile Pro His Ser Asp Gln Arg Leu Arg Pro Gln Arg Thr Lys Gln  
                   20                  25                  30

Tyr Val

&lt;210&gt; 1215

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1215

Ala Arg Leu Asn Val Gly Arg Glu Ser Leu Lys Arg Glu Met Leu Lys  
       1                  5                  10                  15

Ser Gln Gly Val Lys Val Ser Glu Ser Pro Met Gly Ala Arg His Ser  
                   20                  25                  30

Ser Trp Pro Glu Gly Ala Ala Phe Cys Lys Lys Val Gln Gly Ala Gln  
                   35                  40                  45

Met Gln Phe Pro Pro Arg Arg  
       50                  55

&lt;210&gt; 1216

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1216

Ala Arg Leu Asn Val Gly Arg Glu Ser Leu Lys Arg Glu Met Leu  
       1                  5                  10                  15

&lt;210&gt; 1217

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1217

Leu Lys Ser Gln Gly Val Lys Val Ser Glu Ser Pro Met Gly Ala Arg  
       1                  5                  10                  15

602

His Ser Ser Trp  
20

<210> 1218  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 1218  
Ala Phe Cys Lys Lys Val Gln Gly Ala Gln Met Gln Phe Pro Pro Arg  
1 5 10 15

Arg

<210> 1219  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 1219  
Ala Phe Cys Lys Lys Val Gln Gly Ala Gln Met Gln Phe Pro Pro Arg  
1 5 10 15

Arg

<210> 1220  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 1220  
Asn Phe Phe Phe Val Cys Leu Phe Lys Ser Ser Leu Arg Leu Val Asn  
1 5 10 15

Ser Ser Tyr Thr Pro Ile Leu Cys Val Leu  
20 25

<210> 1221  
<211> 37  
<212> PRT  
<213> Homo sapiens

<400> 1221  
Val Gln Val Leu Glu Gln Leu Thr Asn Asn Ala Val Ala Glu Ser Arg  
1 5 10 15

Phe Asn Asp Ala Ala Tyr Tyr Tyr Trp Met Leu Ser Met Gln Cys Leu  
20 25 30

Asp Ile Ala Gln Asp  
35



603

&lt;210&gt; 1222

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1222

Pro Ala Gln Lys Asp Thr Met Leu Gly Lys Phe Tyr His Phe Gln Arg  
 1 5 10 15

Leu Ala Glu Leu Tyr His Gly Tyr His Ala Ile His Arg His Thr Glu  
 20 25 30

Asp Pro

&lt;210&gt; 1223

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1223

Leu Ala Lys Gln Ser Lys Ala Leu Gly Ala Tyr Arg Leu Ala Arg His  
 1 5 10 15

Ala Tyr Asp Lys Leu Arg Gly Leu Tyr Ile Pro  
 20 25

&lt;210&gt; 1224

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1224

Ala Arg Phe Gln Lys Ser Ile Glu Leu Gly Thr Leu Thr Ile Arg Ala  
 1 5 10 15

Lys Pro Phe His Asp Ser Glu Glu Leu Val Pro Leu Cys Tyr Arg Cys  
 20 25 30

Ser Thr Asn Asn  
 35

&lt;210&gt; 1225

&lt;211&gt; 73

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1225

Pro Leu Leu Asn Asn Leu Gly Asn Val Cys Ile Asn Cys Arg Gln Pro  
 1 5 10 15

Phe Ile Phe Ser Ala Ser Ser Tyr Asp Val Leu His Leu Val Glu Phe  
 20 25 30

604

Tyr Leu Glu Glu Gly Ile Thr Asp Glu Glu Ala Ile Ser Leu Ile Asp  
 35 40 45

Leu Glu Val Leu Arg Pro Lys Arg Asp Asp Arg Gln Leu Glu Ile Cys  
 50 55 60

Lys Gln Gln Leu Pro Asp Ser Cys Gly  
 65 70

&lt;210&gt; 1226

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1226

Met Pro Tyr Ala Gln Trp Leu Ala Glu Asn Asp Arg Phe Glu Glu Ala  
 1 5 10 15

Gln Lys Ala Phe His Lys Ala Gly Arg Gln Arg Glu Ala  
 20 25

&lt;210&gt; 1227

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1227

Phe Ser Val His Arg Pro Glu Thr Leu Phe Asn Ile Ser Arg Phe Leu  
 1 5 10 15

Leu His Ser Leu Pro Lys Asp Thr Pro Ser Gly Ile Ser Lys Val Lys  
 20 25 30

Ile Leu Phe Thr  
 35

&lt;210&gt; 1228

&lt;211&gt; 1384

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 1228

ggcacgagcg ttttcgggcc gtgcgtttgt ggccgtccgg cctccctgac atgcagccct 60  
 ctggaccccg aggttggaacc ctactgtgac acacctacca tgcggacact cttcaacctc 120  
 ctctggcttg ccttggcctg cagccctgtt cacactaccc tgtcaaagtc agatgccaaa 180  
 aaagccgcct caaagacgct gctggagaag agtcagtttt cagataagcc ggtgcaagac 240  
 cgggggtttgg tgggtgacgga cctcaaagct gagagtgtgg ttcttgagca tcgcagctac 300  
 tgctcggcaa aggcccggga cagacacttt gctgggggatg tactgggcta tgtcactcca 360

605

|   |      |
|---|------|
| tggaacagcc atggctacga tgtcaccaag gtctttggga gcaagttcac acagatctca   | 420  |
| cccgtctggc tgcagctgaa gagacgtggc cgtgagatgt ttgagggtcac gggcctccac  | 480  |
| gacgtggacc aagggtggat gcgagctgtc aggaagcatg ccaagggcct gcacatagt    | 540  |
| cctcggctcc tgtttgagga ctggacttac gatgatttcc ggaacgtctt agacagt      | 600  |
| gatgagatag aggagctgag caagaccgtg gtccaggtgg caaagaacca gcatttcgat   | 660  |
| ggcttcgtgg tggaggtctg gaaccagctg ctaagccaga agcgcggtgg cctcatccac   | 720  |
| atgtcacccc acttggccga ggctctgcac caggcccgcc tgctggccct cctgggtcac   | 780  |
| ccgcctgcca tcacccccgg gaccgaccag ctgggcatgt tcacgcacaa ggagtttgag   | 840  |
| cagctggccc ccgtgctgga tggtttcagc ctcagtacct acgactactc tacagcgcat   | 900  |
| cagcctggcc ctaatgcacc cctgtcctgg gttcgagcct gcgtccaggt cctggacccg   | 960  |
| aagtccaagt ggcgaagcaa aatcctcctg gggctcaact tctatggtac atccagacac   | 1020 |
| tgaaggacca caggcccccgg atggtgtggg acagccaggt ctcagagcac ttcttcgagt  | 1080 |
| acaagaagag ccgcagtgagg aggcacgtcg tcttctaccc aacctgaag tccctgcagg   | 1140 |
| tgcggctgga gctggcccgg gagctgggag ttgggggtctc tatctgggag ctgggcccagg | 1200 |
| gcctggacta cttctacgac ctgctctagg tgggcattgc ggcctccgag gtggacgtgt   | 1260 |
| tcttttctaa gccatggagt gagtgagcag gtgtgaaata caggcctcca ctccgaaaaa   | 1320 |
| aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa    | 1380 |
| aaaa  | 1384 |

&lt;210&gt; 1229

&lt;211&gt; 1334

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1268)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 1229

|  |     |
|--|-----|
| gcgtggagc gttttccggc cgtgcgtttg tggcgtccg gcctccctga catgcagccc    | 60  |
| tctggacccc gaggttgagc cctactgtga cacacctacc atgcggacac tcttcaacct  | 120 |
| cctctggctt gccctggcct gcagccctgt tcacactacc ctgtcaaagt cagatgccaa  | 180 |
| aaaagccgcc tcaaagacgc tgctggagaa gagtcagttt tcagataagc cgggtgcaaga | 240 |
| ccgggggttg gtggtgacgg acctcaaagc tgagagtgtg gttcttgagc atcgcagcta  | 300 |

|  |      |
|--|------|
| ctgctcggca aaggcccggg acagacactt tgctggggat gtactgggct atgtcactcc  | 360  |
| atggaacagc catggctacg atgtcaccaa ggtctttggg agcaagttca cacagatctc  | 420  |
| acccgtctgg ctgcagctga agagacgtgg ccgtgagatg tttgaggtca cgggcctcca  | 480  |
| cgacgtggac caaggggtga tgcgagctgt caggaagcat gccaaaggcc tgcacatagt  | 540  |
| gcctcggctc ctgtttgagg actggactta cgatgatttc cggaacgtct tagacagtga  | 600  |
| ggatgagata gaggagctga gcaagaccgt ggtccagggt gcaaagaacc agcatttcga  | 660  |
| tggettctgt gtggaggtct ggaaccagct gctaagccag aagcgcgtga ccgaccagct  | 720  |
| gggcatgttc acgcacaagg agtttgagca gctggccccc gtgctggatg gtttcagcct  | 780  |
| catgacctac gactactcta cagcgcatca gcctggccct aatgcacccc tgcctgggt   | 840  |
| tcgagcctgc gtccagggtcc tggaccgaa gtccaagtgg cgaagcaaaa tcctcctggg  | 900  |
| gctcaacttc tatggtatgg actacgcgac ctccaaggat gcccgtagc ctgttgctgg   | 960  |
| ggccaggtag atccagacac tgaaggacca caggccccgg atggtgtggg acagccaggy  | 1020 |
| ctcagagcac ttcttcgagt acaagaagag ccgcagtggg aggcacgtcg tcttctaccc  | 1080 |
| aaccctgaag tccttcgagg tgcggctgga gctggcccg gagctgggcg ttgggggtctc  | 1140 |
| tatctgggag ctgggcccagg gcctggacta cttctacgac ctgctctagg tgggcattgc | 1200 |
| ggcctccgcg gtggacgtgt tcttttctaa gccatggagt gagtgagcag gtgtgaaata  | 1260 |
| caggcctnca ctccgttcaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa  | 1320 |
| aaaaaaaaact cgag   | 1334 |

&lt;210&gt; 1230

&lt;211&gt; 1112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1022)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1079)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 1230

|   |    |
|---|----|
| ggcgttttcc ggccgtgcgt ttgtggccgt ccggcctccc tgacatgcag ccctctggac | 60 |
|---|----|

|   |     |
|---|-----|
| cccgaggttg gaccctactg tgacacacct accatgcgga cactcttcaa cctcctctgg | 120 |
|---|-----|

cttgccctgg cctgcagccc tgttcacact accctgtcaa agtcagatgc caaaaaagcc 180  
gcctcaaaga cgctgctgga gaagagtcag ttttcagata agccgggtgca agaccggggg 240  
ttggtggtga cggacctcaa agctgagagt gtggttcttg agcatcgag ctactgctcg 300  
gcaaaggccc gggacagaca ctttctgctgg gatgtactgg gctatgtcac tccatggaac 360  
agccatggct acgatgtcac caaggtcttt gggagcaagt tcacacagat ctcacccgtc 420  
tggtgcagc tgaagagacg tggccgtgag atgtttgagg tcacgggcct ccacgacgtg 480  
gaccaagggt ggatgcgagc tgtcaggaag catgccaaagg gcctgcacat agtgcctcgg 540  
ctcctgtttg aggactggac ttacgatgat ttccggaacg tcttagacag tgaggatgag 600  
atagaggagc tgagcaagac cgtggtccag gtggcaaaga accagcattt cgatggcttc 660  
gtggtggagg tctggaacca gctgctaagc cagaagcgcg tgggcctcat ccacatgctc 720  
accacttg cggaggtctt gcaccaggcc cggctgctgg ccctcctggt catcccgcct 780  
gccatcacc cccggaccga ccagctgggc atgttcacgc acaaggagtt tgagcagctg 840  
gccccgtgc tggatggttt cagcctcatg acctacgact actctacagc gcatcagcct 900  
ggccctaata caccctgtc ctgggttcga gcctgcgtcc aggtcctgga cccgaartyc 960  
aagtggcgaa caaaatctc ctggggstca acttctatgg watggactam ggcacytcca 1020  
anggatgccc gtkarcctgt tgcggggsc aggtamatyc agamactgaa rgaccacang 1080  
ccccgatgg tgttgacag caagcctcaa ag 1112

<210> 1231

<211> 2474

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2316)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2382)

<223> n equals a,t,g, or c

<220>

608

&lt;221&gt; SITE

&lt;222&gt; (2447)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 1231

|  |      |
|--|------|
| ataagagaca gcgtcagggg ggcggagcct atggaaaaac gccagcaacg cggnccttttt | 60   |
| acggttcctg gccttttget ggccttttgc tcacatgttc tttcctgcgt tatccctga   | 120  |
| ttctgtggat aaccgtatta ccgcctttga gtgagctgat accgctcgcc gcagccgaac  | 180  |
| gaccgagcgc agcgagtcag tgagcgagga agcggaagag cgccaatac gcaaaccgcc   | 240  |
| tctccccgcg cgttggccga ttcattaatg cagctggcac gacaggtttc ccgactggaa  | 300  |
| agcgggcagt gagcgcaacg caattaatgt gagttagctc actcattagg caccacaggc  | 360  |
| tttacacttt atgcttccgg ctcgatatgt gtgtggaatt gtgagcggat aacaatttca  | 420  |
| cacaggaaac agctatgacc atgattacgc caagctcgaa attaaccctc actaaaggga  | 480  |
| acaaaagctg gagctccacc gcggtggcgg ccgctctaga actagtggat ccccgggct   | 540  |
| gcaggaattc ggcacgaggt ccggcctccc tgacatgcag atttccaccc agaagacaga  | 600  |
| gaaggagcca gtggtcatgg aatgggctgg ggtcaaagac tgggtgcctg ggagctgagg  | 660  |
| cagccaccgt ttcagcctgg ccagccctct ggaccccgag gttggaccct actgtgacac  | 720  |
| acctaccatg cggacactct tcaacctcct ctggcttgcc ctggcctgca gccctgttca  | 780  |
| cactaccctg tcaaagtcag atgccaaaa agccgcctca aagacgctgc tggagaagag   | 840  |
| tcagttttca gataagccgg tgcaagaccg gggtttggtg gtgacggacc tcaaagctga  | 900  |
| gagtgtgggt cttgagcatc gcagctactg ctcgccaaag gcccgggaca gacactttgc  | 960  |
| tggggatgta ctgggctatg tcactccatg gaacagccat ggctacgatg tcaccaaggt  | 1020 |
| ctttgggagc aagttcacac agatctcacc cgtctggctg cagctgaaga gacgtggccg  | 1080 |
| tgagatgttt gaggtcacgg gcctccacga cgtggaccaa ggggtgatgc gagctgtcag  | 1140 |
| gaagcatgcc aagggcctgc acatagtgcc tcggctcctg tttgaggact ggacttacga  | 1200 |
| tgatttccgg aacgtcttag acagtgagga tgagatagag gagctgagca agaccgtgg   | 1260 |
| ccaggtggca aagaaccagc atttcgatgg ctctgtgggt gaggtctgga accagctgct  | 1320 |
| aagccagaag cgcgtgggcc tcatccacat gctcaccac ttggccgagg ctctgcacca   | 1380 |
| ggcccggtg ctggccctcc tggatcatcc gcctgccatc acccccgga ccgaccagct    | 1440 |
| gggcatgttc acgcacaagg agtttgagca gctggccccc gtgctggatg gtttcagcct  | 1500 |
| catgacctac gactactcta cagcgcatca gcctggccct aatgcacccc tgtcctgggt  | 1560 |
| tcgagcctgc gtccaggtcc tggacccgaa gtccaagtgg cgaagcaaaa tcctcctggg  | 1620 |

609

gctcaacttc tatggtacat ccagacactg aaggaccaca ggccccggat ggtgtgggac 1680  
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 tttcgccagc tggcgtaata gcgaagaggc ccgcaccgat cgcccttccc aacagttgag 2160  
 cagcctgaat ggcgaatggc aaattgtaag cgtaaatatt ttgttaaaat tcgcgtaaa 2220  
 tttttgttaa atcagctcat tttttaacca ataggccgaa atcggcaaaa tcccttataa 2280  
 atcaaaagaa tagaccgaga tagggttgag tggtgntcca gtttgaaca agagtccact 2340  
 attaaagaac gtggactcca acgtcaaagg gcgaaaaacc gnctatcagg gcgatggccc 2400  
 actacgtgaa ccatcacctc taatcaaagt tttttggggt cgaggtncct ctaaaagcac 2460  
 ttaatcgga accc 2474

&lt;210&gt; 1232

&lt;211&gt; 307

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1232

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro  
 1 5 10 15

Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys  
 20 25 30

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
 35 40 45

Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
 50 55 60

Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp  
 65 70 75 80

Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr  
 85 90 95

Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln

610

| 100  | 105 | 110 |
|--|-----|-----|
| Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp<br>115 120 125     |     |     |
| Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu<br>130 135 140     |     |     |
| His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe<br>145 150 155 160 |     |     |
| Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr<br>165 170 175     |     |     |
| Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu<br>180 185 190     |     |     |
| Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met<br>195 200 205     |     |     |
| Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu<br>210 215 220     |     |     |
| Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met<br>225 230 235 240 |     |     |
| Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe<br>245 250 255     |     |     |
| Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn<br>260 265 270     |     |     |
| Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys<br>275 280 285     |     |     |
| Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Thr<br>290 295 300     |     |     |
| Ser Arg His<br>305   |     |     |

&lt;210&gt; 1233

&lt;211&gt; 363

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (307)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 1233

|   |
|---|
| Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro |
| 1 5 10 15   |

|   |
|---|
| Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys |
| 20 25 30  |



611

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
 35 40 45  
 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
 50 55 60  
 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp  
 65 70 75 80  
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr  
 85 90 95  
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln  
 100 105 110  
 Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp  
 115 120 125  
 Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu  
 130 135 140  
 His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe  
 145 150 155 160  
 Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr  
 165 170 175  
 Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu  
 180 185 190  
 Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Thr Asp Gln Leu Gly  
 195 200 205  
 Met Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly  
 210 215 220  
 Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro  
 225 230 235 240  
 Asn Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro  
 245 250 255  
 Lys Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly  
 260 265 270  
 Met Asp Tyr Ala Thr Ser Lys Asp Ala Arg Glu Pro Val Val Gly Ala  
 275 280 285  
 Arg Tyr Ile Gln Thr Leu Lys Asp His Arg Pro Arg Met Val Trp Asp  
 290 295 300  
 Ser Gln Xaa Ser Glu His Phe Phe Glu Tyr Lys Lys Ser Arg Ser Gly  
 305 310 315 320  
 Arg His Val Val Phe Tyr Pro Thr Leu Lys Ser Leu Gln Val Arg Leu  
 325 330 335

612

Glu Leu Ala Arg Glu Leu Gly Val Gly Val Ser Ile Trp Glu Leu Gly  
340 345 350

Gln Gly Leu Asp Tyr Phe Tyr Asp Leu Leu Xaa  
355 360

<210> 1234

<211> 321

<212> PRT

<213> Homo sapiens

**<220>**

**<221> SITE**

<222> (289)

<223> Xaa equals any of the naturally occurring L-amino acids

 $\langle 220 \rangle$ 

<221> SITE

<222> (303)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

**<221> SITE**

<222> (306)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

**<221> SITE**

<222> (308)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (310)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

<221> SITE

<222> (314)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

<221> SITE

<222> (319)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

&lt;221&gt; SITE

$\langle 222 \rangle$  (321)

<223> Xaa equals any of the naturally occurring L-amino acids

**<400> 1234**

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro  
1 5 10 15

Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys  
20 25 30

613

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
 35 40 45  
 Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
 50 55 60  
 Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp  
 65 70 75 80  
 Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr  
 85 90 95  
 Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln  
 100 105 110  
 Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp  
 115 120 125  
 Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu  
 130 135 140  
 His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe  
 145 150 155 160  
 Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr  
 165 170 175  
 Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu  
 180 185 190  
 Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met  
 195 200 205  
 Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu  
 210 215 220  
 Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met  
 225 230 235 240  
 Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe  
 245 250 255  
 Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn  
 260 265 270  
 Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys  
 275 280 285  
 Xaa Lys Trp Arg Thr Lys Ser Ser Trp Gly Ser Thr Ser Met Xaa Trp  
 290 295 300  
 Thr Xaa Arg Xaa Pro Xaa Asp Ala Arg Xaa Pro Val Val Gly Xaa Arg  
 305 310 315 320  
 Xaa

614

&lt;210&gt; 1235

&lt;211&gt; 307

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1235

Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro  
 1 5 10 15

Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys  
 20 25 30

Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
 35 40 45

Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
 50 55 60

Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp  
 65 70 75 80

Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr Asp Val Thr  
 85 90 95

Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val Trp Leu Gln  
 100 105 110

Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Val Thr Gly Leu His Asp  
 115 120 125

Val Asp Gln Gly Trp Met Arg Ala Val Arg Lys His Ala Lys Gly Leu  
 130 135 140

His Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr Asp Asp Phe  
 145 150 155 160

Arg Asn Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu Ser Lys Thr  
 165 170 175

Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe Val Val Glu  
 180 185 190

Val Trp Asn Gln Leu Leu Ser Gln Lys Arg Val Gly Leu Ile His Met  
 195 200 205

Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu Leu Ala Leu  
 210 215 220

Leu Val Ile Pro Pro Ala Ile Thr Pro Gly Thr Asp Gln Leu Gly Met  
 225 230 235 240

Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Val Leu Asp Gly Phe  
 245 250 255

Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ala His Gln Pro Gly Pro Asn  
 260 265 270

615

Ala Pro Leu Ser Trp Val Arg Ala Cys Val Gln Val Leu Asp Pro Lys  
 275 280 285

Ser Lys Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe Tyr Gly Thr  
 290 295 300

Ser Arg His  
 305

<210> 1236

<211> 17

<212> PRT

<213> Homo sapiens

<400> 1236

Gly Ile Val Ala Phe Ile Val Phe Leu Leu Leu Ile Met Leu Ile Phe  
 1 5 10 15

Leu

<210> 1237

<211> 367

<212> PRT

<213> Homo sapiens

<400> 1237

Met Gly Ala Pro Ala Ala Ser Leu Leu Leu Leu Leu Leu Phe Ala  
 1 5 10 15

Cys Cys Trp Ala Pro Gly Gly Ala Asn Leu Ser Gln Asp Gly Tyr Trp  
 20 25 30

Gln Glu Gln Asp Leu Glu Leu Gly Thr Leu Ala Pro Leu Asp Glu Ala  
 35 40 45

Ile Ser Ser Thr Trp Ser Ser Pro Asp Met Leu Ala Ser Gln Asp Ser  
 50 55 60

Gln Pro Trp Thr Ser Asp Glu Thr Val Val Ala Gly Gly Thr Val Val  
 65 70 75 80

Leu Lys Cys Gln Val Lys Asp His Glu Asp Ser Ser Leu Gln Trp Ser  
 85 90 95

Asn Pro Ala Gln Gln Thr Leu Tyr Phe Gly Glu Lys Arg Ala Leu Arg  
 100 105 110

Asp Asn Arg Ile Gln Leu Val Thr Ser Thr Pro His Glu Leu Ser Ile  
 115 120 125

Ser Ile Ser Asn Val Ala Leu Ala Asp Glu Gly Glu Tyr Thr Cys Ser  
 130 135 140

Ile Phe Thr Met Pro Val Arg Thr Ala Lys Ser Leu Val Thr Val Leu  
 145 150 155 160

616

Gly Ile Pro Gln Lys Pro Ile Ile Thr Gly Tyr Lys Ser Ser Leu Arg  
 165 170 175  
 Glu Lys Asp Thr Ala Thr Leu Asn Cys Gln Ser Ser Gly Ser Lys Pro  
 180 185 190  
 Ala Ala Arg Leu Thr Trp Arg Lys Gly Asp Gln Glu Leu His Gly Glu  
 195 200 205  
 Pro Thr Arg Ile Gln Glu Asp Pro Asn Gly Lys Thr Phe Thr Val Ser  
 210 215 220  
 Ser Ser Val Thr Phe Gln Val Thr Arg Glu Asp Asp Gly Ala Ser Ile  
 225 230 235 240  
 Val Cys Ser Val Asn His Glu Ser Leu Lys Gly Ala Asp Arg Ser Thr  
 245 250 255  
 Ser Gln Arg Ile Glu Val Leu Tyr Thr Pro Thr Ala Met Ile Arg Pro  
 260 265 270  
 Asp Pro Pro His Pro Arg Glu Gly Gln Lys Leu Leu Leu His Cys Glu  
 275 280 285  
 Gly Arg Gly Asn Pro Val Pro Gln Gln Tyr Leu Trp Glu Lys Glu Gly  
 290 295 300  
 Ser Val Pro Pro Leu Lys Met Thr Gln Glu Ser Ala Leu Ile Phe Pro  
 305 310 315 320  
 Phe Leu Asn Lys Ser Asp Ser Gly Thr Tyr Gly Cys Thr Ala Thr Ser  
 325 330 335  
 Asn Met Gly Ser Tyr Lys Ala Tyr Tyr Thr Leu Asn Val Asn Asp Pro  
 340 345 350  
 Ser Pro Val Pro Ser Ser Ser Ser Thr Tyr His Ala Ile Ile Gly  
 355 360 365

&lt;210&gt; 1238

&lt;211&gt; 344

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1238

Asn Leu Ser Gln Asp Gly Tyr Trp Gln Glu Gln Asp Leu Glu Leu Gly  
 1 5 10 15  
 Thr Leu Ala Pro Leu Asp Glu Ala Ile Ser Ser Thr Val Trp Ser Ser  
 20 25 30  
 Pro Asp Met Leu Ala Ser Gln Asp Ser Gln Pro Trp Thr Ser Asp Glu  
 35 40 45  
 Thr Val Val Ala Gly Gly Thr Val Val Leu Lys Cys Gln Val Lys Asp  
 50 55 60

617

His Glu Asp Ser Ser Leu Gln Trp Ser Asn Pro Ala Gln Gln Thr Leu  
 65 70 75 80  
 Tyr Phe Gly Glu Lys Arg Ala Leu Arg Asp Asn Arg Ile Gln Leu Val  
 85 90 95  
 Thr Ser Thr Pro His Glu Leu Ser Ile Ser Ile Ser Asn Val Ala Leu  
 100 105 110  
 Ala Asp Glu Gly Glu Tyr Thr Cys Ser Ile Phe Thr Met Pro Val Arg  
 115 120 125  
 Thr Ala Lys Ser Leu Val Thr Val Leu Gly Ile Pro Gln Lys Pro Ile  
 130 135 140  
 Ile Thr Gly Tyr Lys Ser Ser Leu Arg Glu Lys Asp Thr Ala Thr Leu  
 145 150 155 160  
 Asn Cys Gln Ser Ser Gly Ser Lys Pro Ala Ala Arg Leu Thr Trp Arg  
 165 170 175  
 Lys Gly Asp Gln Glu Leu His Gly Glu Pro Thr Arg Ile Gln Glu Asp  
 180 185 190  
 Pro Asn Gly Lys Thr Phe Thr Val Ser Ser Ser Val Thr Phe Gln Val  
 195 200 205  
 Thr Arg Glu Asp Asp Gly Ala Ser Ile Val Cys Ser Val Asn His Glu  
 210 215 220  
 Ser Leu Lys Gly Ala Asp Arg Ser Thr Ser Gln Arg Ile Glu Val Leu  
 225 230 235 240  
 Tyr Thr Pro Thr Ala Met Ile Arg Pro Asp Pro Pro His Pro Arg Glu  
 245 250 255  
 Gly Gln Lys Leu Leu Leu His Cys Glu Gly Arg Gly Asn Pro Val Pro  
 260 265 270  
 Gln Gln Tyr Leu Trp Glu Lys Glu Gly Ser Val Pro Pro Leu Lys Met  
 275 280 285  
 Thr Gln Glu Ser Ala Leu Ile Phe Pro Phe Leu Asn Lys Ser Asp Ser  
 290 295 300  
 Gly Thr Tyr Gly Cys Thr Ala Thr Ser Asn Met Gly Ser Tyr Lys Ala  
 305 310 315 320  
 Tyr Tyr Thr Leu Asn Val Asn Asp Pro Ser Pro Val Pro Ser Ser Ser  
 325 330 335  
 Ser Thr Tyr His Ala Ile Ile Gly  
 340

&lt;210&gt; 1239

&lt;211&gt; 24

618

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1239

Met Gly Ala Pro Ala Ala Ser Leu Leu Leu Leu Leu Leu Phe Ala  
1 5 10 15

Cys Cys Trp Ala Pro Gly Gly Ala  
20

&lt;210&gt; 1240

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1240

Asp Gly Tyr Trp Gln Glu Gln Asp Leu Glu Leu Gly Thr Leu Ala Pro  
1 5 10 15

Leu Asp Glu Ala Ile Ser Ser Thr Trp Ser Ser Pro Asp Met Leu Ala  
20 25 30

Ser Gln

&lt;210&gt; 1241

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1241

Asn Leu Ser Gln Asp Gly Tyr Trp Gln Glu Gln Asp Leu Glu Leu Gly  
1 5 10 15

Thr Leu Ala Pro Leu Asp Glu Ala Ile Ser Ser Thr Trp Ser Ser Pro  
20 25 30

Asp Met Leu Ala Ser Gln Asp Ser Gln Pro  
35 40

&lt;210&gt; 1242

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1242

Asn Leu Ser Gln Asp Ser Gln Pro  
1 5

&lt;210&gt; 1243

&lt;211&gt; 63



619

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1243

Met Gly Ala Pro Ala Ala Ser Leu Leu Leu Leu Leu Leu Phe Ala  
 1 5 10 15

Cys Cys Trp Ala Pro Gly Gly Ala Asn Leu Ser Gln Asp Asp Ser Gln  
 20 25 30

Pro Trp Thr Ser Asp Glu Thr Val Val Ala Gly Gly Thr Val Val Leu  
 35 40 45

Lys Cys Gln Val Lys Asp His Glu Asp Ser Ser Leu Gln Trp Ser  
 50 55 60

&lt;210&gt; 1244

&lt;211&gt; 1542

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1445)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1515)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1520)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1535)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 1244

|            |            |            |            |            |             |     |
|------------|------------|------------|------------|------------|-------------|-----|
| ggcasagcca | cctcggcccc | gggctccgaa | gcggetcggg | ggcgcccttt | cgggtcaacat | 60  |
| cgtagtccac | cccctcccca | tccccagccc | ccggggattc | aggctcgcca | gcgcccagcc  | 120 |
| agggagccgg | ccgggaagcg | cgatgggggc | cccagccgcc | tcgctcctgc | tcctgctcct  | 180 |
| gctgttcgcc | tgctgctggg | cgcccggcgg | ggccaacctc | tcccaggacg | acagccagcc  | 240 |
| ctggacatct | gatgaaacag | tggtggctgg | tggcaccgtg | gtgctcaagt | gccaagtga   | 300 |
| agatcacgag | gactcatccc | tgcaatggtc | ttaaccctgc | tcagcagact | ctctactttg  | 360 |
| gggagaagag | agcccttcga | gataatcgaa | ttcagctggt | tamctctacg | ccccacgagc  | 420 |
| tcagcatcag | catcagcaat | gtggccctgg | cagacgaggg | cgagtacacc | tgctcaatct  | 480 |
| tcactatgcc | tgtgcgaact | gccaagtccc | tcgtcactgt | gctaggaatt | ccacagaagc  | 540 |
| ccatcatcac | tggttataaa | tcttcattac | gggaaaaaga | cacagccacc | ctaaactgtc  | 600 |
| agtcttctgg | gagcaagcct | gcagcccggc | tcacctggag | aaagggtgac | caagaactcc  | 660 |
| acggagaacc | aaccgcgata | caggaagatc | ccaatggtaa | aaccttcact | gtcagcagct  | 720 |
| cggtgacatt | ccaggttacc | cgggaggatg | atggggcgag | catcgtgtgc | tctgtgaacc  | 780 |
| atgaatctct | aaagggagct | gacagatcca | cctctcaacg | cattgaagtt | ttatacacac  | 840 |
| caactgcgat | gattaggcca | gaccctcccc | atcctcgtga | gggccagaag | ctgttgctac  | 900 |

620

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actgtgaggg tcgcggaat ccagtcctcc agcagtagct atgggagaag gagggcagtg      960
tgccacccct gaagatgacc caggagagtg ccctgatctt ccctttcctc aacaagagtg      1020
acagtggcac ctacggctgc acagccacca gcaacatggg cagctacaag gcctactaca      1080
ccctcaatgt taatgacccc agtccggtgc cctcctcctc cagcacctac cagcccatca      1140
tcggtgggat cgtggctttc attgtcttcc tgctgctcat catgctcatc ttccttgccc      1200
actacttgat cgggcacaaa ggaacctacc tgacacatga ggcaaaaggc tccgacgatg      1260
ctccagacgc ggacacggcc atcatcaatg cagaaggcgg gcagtcagga ggggacgaca      1320
agaaggaata tttcatctag aggcgcctgc ccacttcctg cgccccccag ggccttgagg      1380
ggacttgctg gggccgtcac caaccggac ttgtacagag caaccgcagg ggccgscctt      1440
cccgnttggt cccagcccca cccacccct tggtacagaa tgtytkgtt gggtgcggt      1500
tttgtwattg gtttnggatn ggggaaggga ggganggcgg gg                        1542

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&lt;210&gt; 1245

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1245

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Pro Thr Cys Tyr Ser Arg Met Arg Ala Leu Ser Gln Glu Ile Thr Arg
  1                      5                      10                      15

Asp Phe Asn Leu Leu Gln Val Ser Glu Pro Ser Glu Pro Cys Val Arg
          20                      25                      30

Tyr Leu Pro Arg Leu Tyr Leu Asp Ile His Asn Tyr Cys Val Leu Asp
  35                      40                      45

ys Leu Arg Asp Phe Val Ala Ser Pro Pro Cys Trp Lys Val Ala Gln
  50                      55                      60

Val Asp Ser Leu Lys Asp Lys Ala Arg Lys Leu Tyr Thr Ile Met Asn
  65                      70                      75                      80

Ser Phe Cys Arg Arg Asp Leu Val Phe Leu Leu Asp Asp Cys Asn Ala
          85                      90                      95

Leu Glu Tyr Pro Ile Pro Val Thr Thr Val Leu Pro Asp Arg Gln Arg
  100                      105                      110

```

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on page 253, line 12.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit  
February 16, 2001

Accession Number  
PTA-3070

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

|   |                               |  |  |                                   |  |
|---|-------------------------------|--|--|-----------------------------------|--|
|   |                               |  |  |                                   |  |
|   | For receiving Office use only |  |  | For International Bureau use only |  |
| <input type="checkbox"/> This sheet was received with the international application |                               |  | <input type="checkbox"/> This sheet was received by the International Bureau on:<br><div style="text-align: center;">21 MAR 2001</div> |                                   |  |
| Authorized officer  |                               |  | Authorized officer <i>J. N. Adams.</i>   |                                   |  |

**PCT/US01/05614**  
**ATCC Deposit No. PTA-3070**

#### **CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

#### **NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

#### **AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations)

#### **FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

PCT/US01/05614  
ATCC Deposit No.: PTA-3070

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

